European Journal of Cell Biology 101 (2022) 151207

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Disease association of cyclase-associated protein (CAP): Lessons from gene-targeted mice and human genetic studies

Marco B. Rust [a,b,c,*], Elena Marcello [d,**]

[a] Molecular Neurobiology Group, Institute of Physiological Chemistry, Philipps-University of Marburg, 35032 Marburg, Germany
[b] Center for Mind, Brain and Behavior (CMBB), University of Marburg and Justus-Liebig-University Giessen, 35032 Marburg, Germany
[c] DFG Research Training Group 'Membrane Plasticity in Tissue Development and Remodeling', GRK 2213, Philipps-University of Marburg, 35032 Marburg, Germany
[d] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, 20133 Milan, Italy

ARTICLE INFO

Keywords:
Cyclase-associated protein
SRV2
Actin dynamics
CAP1
CAP2

ABSTRACT

Cyclase-associated protein (CAP) is an actin binding protein that has been initially described as partner of the adenylyl cyclase in yeast. In all vertebrates and some invertebrate species, two orthologs, named CAP1 and CAP2, have been described. CAP1 and CAP2 are characterized by a similar multidomain structure, but different expression patterns. Several molecular studies clarified the biological function of the different CAP domains, and they shed light onto the mechanisms underlying CAP-dependent regulation of actin treadmilling. However, CAPs are crucial elements not only for the regulation of actin dynamics, but also for signal transduction pathways. During recent years, human genetic studies and the analysis of gene-targeted mice provided important novel insights into the physiological roles of CAPs and their involvement in the pathogenesis of several diseases. In the present review, we summarize and discuss recent progress in our understanding of CAPs' physiological functions, focusing on heart, skeletal muscle and central nervous system as well as their involvement in the mechanisms controlling metabolism. Remarkably, loss of CAPs or impairment of CAPs-dependent pathways can contribute to the pathogenesis of different diseases. Overall, these studies unraveled CAPs complexity highlighting their capability to orchestrate structural and signaling pathways in the cells.

1. Introduction

Cyclase-associated protein (CAP) is a highly conserved, multidomain protein, which has been first cloned from the baker's yeast *Saccharomyces* (*S.*) *cerevisiae* more than 30 years ago (Field et al., 1990). Initially, it was identified as a protein that binds to adenylyl cyclase in yeast, and it therefore has been named cyclase-associated protein (Field et al., 1988). Apart from its adenylyl cyclase association, early yeast studies implicated CAP in the activation of the RAS-family GTPase Ras-like protein 2 (RAS2) (Fedor-Chaiken et al., 1990; Field et al., 1990). These studies showed that mutant yeast CAP variants suppressed a phenotype (heat shock and nitrogen starvation sensitivity) elicited by the hyperactive RAS2 variant RAS2-V19, explaining why yeast homologs were independently named SRV2 (suppressor of Ras2-Val19). Subsequent yeast studies revealed additional phenotypes including impaired growth and altered morphology in CAP mutant strains that were not present in strains with impaired RAS2/adenylyl cyclase pathways (Fedor-Chaiken et al., 1990; Field et al., 1990; Vojtek et al., 1991). These findings suggested the existence of RAS2/adenylyl cyclase-independent CAP functions, which were later assigned to its function in actin cytoskeleton regulation (Hubberstey and Mottillo, 2002; Zelicof et al., 1993).

Since these initial studies, CAP orthologs have been identified in all eukaryotic species examined. It has been shown that most invertebrates possess only one CAP, while vertebrates and some invertebrates such as *Caenorhabditis* (*C.*) *elegans* have two family members with different expression patterns (for review: Ono, 2013; Rust et al., 2020). To date, CAP functions have been investigated in various animal models including *C. elegans*, *Drosophila* (*D.*) *melanogaster* and mouse as well as in a variety of cellular systems (for review: Ono, 2013; Rust et al., 2020). Collectively, these studies revealed that CAP's association with adenylyl cyclase and its actin functions are both conserved from yeast to mammals, and they led actin cytoskeleton regulation emerge as its predominant molecular function. Advanced by studies of the past few years (Johnston et al., 2015; Kotila et al., 2018, 2019; Shekhar et al., 2019), it

* Correspondence to: Corresponding authorInstitute of Physiological Chemistry, Philipps-University of Marburg, 35032 Marburg, Germany.
** Corresponding author.
E-mail addresses: rust@uni-marburg.de (M.B. Rust), elena.marcello@unimi.it (E. Marcello).

https://doi.org/10.1016/j.ejcb.2022.151207
Received 17 December 2021; Received in revised form 4 February 2022; Accepted 7 February 2022
Available online 8 February 2022

Nomenclature

ABL Abelson murine leukemia viral oncogene homolog
ABP Actin-binding protein
ABP1 Actin-binding protein 1
AC3 Adenylyl cyclase 3
ADF Actin-depolymerizing factor
ADF-H domain Actin depolymerizing factor homology domain
ADP Adenosine diphosphate
Arp2/3 complex Actin-related protein 2/3 complex
ATP Adenosine triphosphate
cAMP Cyclic adenosine monophosphate
CAP Cyclase-associated protein
CAP1 Cyclase-associated protein 1
CAP2 Cyclase-associated protein 2
CARP domain CAP and RP2 domain
CAS-1 Muscle-enriched CAP ortholog of *C. elegans*
CAS-2 Non-muscle CAP ortholog of *C. elegans*
CNS Central nervous system
C. elegans *Caenorhabditis elegans*
CMTD Charcot-Marie-Tooth disease
Co-IP Co-immunoprecipitation
Cys Cysteine residue
DAD Diaphanous autoregulatory domain
DCM Dilated cardiomyopathy
DID Diaphanous inhibitory domain
D. melanogaster *Drosophila melanogaster*
E Embryonic day of mouse development
ECG Electrocardiogram
Ena Enabled
EUCOMM European Conditional Mouse Mutagenesis Program
F-actin Filamentous actin
FSGS Focal segmental glomerulosclerosis
G-actin Globular actin monomer
GTP guanosine triphosphate
HFD Helical-folded domain
INF2 Inverted formin 2
KAc-actin Lysine-acetylated actin
KO Knockout
KD Knockdown
LDL Low-density lipoprotein
LDLR Low-density lipoprotein receptor
Lmod Leiomodin
LTP Long-term potentiation
MRTF Myocardin-related transcription factor
NF-κB Nuclear factor 'κ-light-chain-enhancer' of activated B-cells
OD Oligomerization domain
P1 Proline-rich motif 1
P2 Proline-rich motif 2
PCSK9 Proprotein convertase subtilisin/kexin type-9
PKA Protein kinase A
P_i Inorganic phosphate
RAS2 Ras-like protein 2
RLE motif Arg-Leu-Glu repeats
RP2 Retinitis pigmentosa protein 2
S. cerevisiae *Saccharomyces cerevisiae*
SCD Sudden cardiac death
Ser Serine residue
SH3 Src homology 3
SRF Serum response factor
SRV2 Suppressor of Ras2-Val19
SVT Supraventricular tachycardia
Tcap Telethonin
TCF Ternary complex factor
TIRF microscopy total internal reflections fluorescence microscopy
Tmod Tropomodulin
UNC-60A Non-muscle ADF/cofilin ortholog of *C. elegans*
UNC-60B Muscle-enriched ADF/Cofilin ortholog of *C. elegans*
Val Valine residue
VASP Vasodilator-stimulated phosphoprotein
WASP Wiscott-Aldrich-Syndrome protein
WH2 domain WASP homology 2 domain

is now well-accepted that CAP accelerates various crucial steps of the actin treadmilling mechanisms, including subunit dissociation from filamentous actin (F-actin) and nucleotide exchange on globular actin monomers (G-actin). Moreover, functional interactions with several established actin regulators such as actin depolymerizing factor (ADF)/cofilin, twinfilin, inverted formin 2 (INF2), profilin or actin-binding protein 1 (ABP1) have been identified (A et al., 2020, 2019; Balcer et al., 2003; Bertling et al., 2007; Johnston et al., 2015; Kotila et al., 2019; Schneider et al., 2021a), which further highlighted CAP's relevance for actin cytoskeleton regulation and increased the complexity of CAP-dependent actin regulatory mechanisms.

Genetic studies in model systems not only confirmed important CAP functions in actin cytoskeleton regulation, but also unraveled crucial developmental and physiological functions ranging from morphogenesis of various tissues including epithelia, striated muscles, eye and brain to cellular communication, metabolism and heart physiology (Benlali et al., 2000; Colpan et al., 2021; Field et al., 2015; Jang et al., 2019; Kepser et al., 2019; Nomura et al., 2012; Peche et al., 2012; Pelucchi et al., 2020b; Schneider et al., 2021a; Wills et al., 2002). Moreover, human genetic studies identified pathogenic CAP2 variants and associated them with clinical symptoms that mirrored phenotypes described for mice lacking CAP2 (Table 1; Aspit et al., 2019; Cheema et al., 2020; Field et al., 2015; Kepser et al., 2019; Patel and Peterson, 2019; Peche et al., 2012; Gurunathan et al., 2021). Together with studies that suggested a contribution of CAP2 inactivation to the rare developmental disorder 6p22 syndrome or implicated CAP in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease or neuropathies such as Charcot-Marie-Tooth disease (CMTD) (A et al., 2020, 2019; Pelucchi et al., 2020b), these findings led CAP emerge as an important regulator of actin remodeling in health and disease. In the present review article, we will summarize current literature on CAP's molecular functions and we will introduce recent reports that associated CAP with diseases, focusing on genetic studies in mice and humans.

2. Molecular functions

A detailed description of CAP's protein domains, their structures and molecular functions has been provided in a comprehensive review article just recently (Rust et al., 2020). We will therefore only briefly introduce the different domains in this chapter, and we will summarize current knowledge of their molecular functions. Hereby, we will primarily focus on yeast CAP and the mammalian orthologs CAP1 and CAP2, which were most intensively studied during recent years. All three proteins are similar in size (526 amino acids in yeast, 474 amino acids in mouse CAP1, 476 amino acids in mouse CAP2) and share a highly conserved structure (Ono, 2013; Rust et al., 2020), which can be sub-divided into three protein regions that can partially act independently of each other: (1) a N-terminal part consisting of the N-terminal oligomerization domain and a helical folded domain (HFD), (2) a central region comprising two proline-rich motifs (P1 and P2, respectively) separated by a Wiscott-Aldrich-Syndrome protein (WASP) homology 2 (WH2) domain, and (3) a C-terminal part that mainly consists of the CAP

Table 1
Summary of human diseases associated with CAP2 mutations and phenotypes in gene-targeted mice. Abbreviations: DCM: dilated cardiomyopathy, SCD: sudden cardiac death, SVT: supraventricular tachycardia.

	Gene	Clinical manifestations	Genetic alteration	Reference
Human	CAP2	DCM narrow complex tachyarrhythmia, SVT, respiratory distress	Nucleotide exchange in donor splice consensus sequence of exon 7 (c636 +1 G>A)	Aspit et al. (2019)
	CAP2	DCM, impaired systolic function, pulmonary atresia	Pathogenic CAP2 variant in fetus not specified	Patel and Peterson (2019)
	CAP2	DCM	Homozygous nonsense mutation at Y316	Cheema et al. (2020)
	CAP2	DCM, impaired systolic function, nemaline myopathy, respiratory failure, hypotension	Homozygous frame shift mutation (c430fs)	Gurunathan et al. (2021)
Mouse	CAP1	Embryonic lethal	Systemic CAP1-KO	Jang et al. (2019)
	CAP1	Increased liver LDLR expression, reduced plasma total cholesterol and LDL cholesterol levels upon high-fat diet	Systemic heterozygous CAP1-KO	Jang et al. (2019)
	CAP1	Impaired neuronal connectivity, perinatal lethality	Brain-specific CAP1-KO	Schneider et al. (2021a)
	CAP2	Growth retardation	Systemic CAP2-KO	Peche et al. (2012);Field et al. (2015); Kepser et al. (2019)
	CAP2	Cardiomyopathy incl. bradycardia, spontaneous ventricular arrhythmias, prolonged conduction times, prolonged PQ and QT intervals,	Systemic CAP2-KO, heart-specific CAP2-KO	Peche et al. (2012);Field et al. (2015); Stockigt et al. (2016);Xiong et al. (2019)
	CAP2	Myopathy characterized by ring fibers, muscle weakness, delay in motor function development	Systemic CAP2-KO	Kepser et al. (2019)
	CAP2	Microphthalmia, sensitivity to eye inflammation and infections	Systemic CAP2-KO	Field et al. (2015)
	CAP2	Wound healing problems	Systemic CAP2-KO	Kosmas et al. (2015)

and retinitis pigmentosa protein 2 (CARP) domain, which harbors a dimerization motif at the most C-terminal part (Fig. 1).

2.1. CAP function in adenylyl cyclase regulation

The N-terminal oligomerization domain is composed of roughly 40 amino acids. It includes Arg-Leu-Glu repeats (RLE motifs) and was predicted to form a coiled-coil structure due to presence of heptad repeat motifs (αXXαXXX), in which α at position 1 and 4 are hydrophobic amino acid residues (Nishida et al., 1998). This domain was sufficient for adenylyl cyclase binding and activation in yeast (Nishida et al., 1998), a CAP function that was assumed for quite some time to be present only in a few fungal species and protists, but absent from higher eukaryotes (Hubberstey and Mottillo, 2002; Ono, 2013). This view has been challenged by recent studies, which revealed functional interaction of CAP1 and adenylyl cyclase in mammals (Quinn et al., 2017; Zhang et al., 2021). By co-immunoprecipitation (Co-IP), either of these two studies showed physical interaction of CAP1 and various adenylyl cyclase isoforms in mouse and human pancreatic adenocarcinoma cells (Quinn et al., 2017). This study further suggested that forskolin, a plant-derived stimulator of adenylyl cyclase activity, forced adenylyl cyclase 3 (AC3) to form a complex with CAP1 and G-actin and that complex formation enhanced production of cyclic adenosine monophosphate (cAMP) and inhibited cell migration and invasion (Quinn et al., 2017). In line with this study, an inhibitory function towards pancreatic cell migration as well as an implication in cAMP signaling downstream of the cytokine resistin has been shown for CAP1 in earlier studies (Lee et al., 2014; Yamazaki et al., 2009). The other of the two studies confirmed interaction of CAP1 with several adenylyl cyclase isoforms in vitro, and it mapped binding to CAP1's N-terminal region (Zhang et al., 2021). This interaction required RLE motifs within the oligomerization domain of CAP1 as well as the conserved catalytic loops C1a and C2a of adenylyl cyclase. Moreover, this study revealed that CAP1 can positively modulate both adenylyl cyclase activation mediated by either forskolin or its physiological activator GαS as well as cellular cAMP levels. Finally, it revealed that CAP1 acts downstream of Rap1, a small GTPase that has been identified as CAP1 interaction partner in a previous study (Zhang et al., 2018), and that CAP1 was relevant for cAMP-mediated proliferation of rat thyroid follicular cells. Rap1's interaction with CAP1 did not require binding of guanosine triphosphate (GTP), but of a geranylgeranyl group that specifically interacts with β-sheets of CAP1's CARP domain (Zhang et al., 2018). This study led prenylation of small GTPases emerge as a common mechanism for their interaction with CAP, since an earlier study demonstrated that farnesylation of yeast Ras increased its association with CAP, and it thereby strongly increased adenylyl cyclase activity (Shima et al., 1997). Together, these studies revealed that an interaction between CAP and adenylyl cyclase as well as a role for CAP in cAMP signaling is conserved from yeast to human (Fig. 2A).

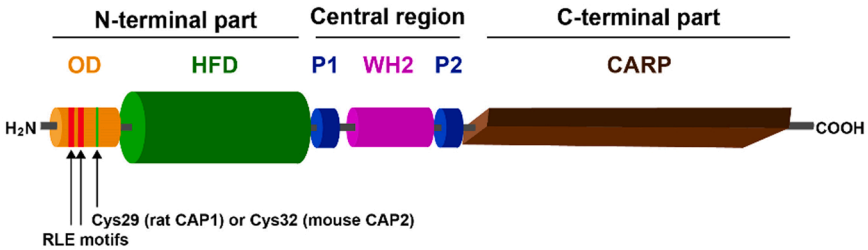

Fig. 1. CAP domain organization. CAP from yeast to mammals can be sub-divided into three protein regions. The N-terminal region comprises the oligomerization domain (OD) and the helical folded domain (HFD). The OD includes two Arg-Leu-Glu repeats (RLE motifs) as well as a cysteine residue relevant for dimer formation. The central region comprises the Wiscott-Aldrich-Syndrome protein (WASP) homology 2 (WH2) domain flanked by two proline-rich motifs (P1 and P2), and the C-terminal region mainly consists of a CAP and retinitis pigmentosa protein 2 (CARP) domain. A detailed description of the protein domains and their molecular activities is provided in chapter 2 'Molecular functions'.

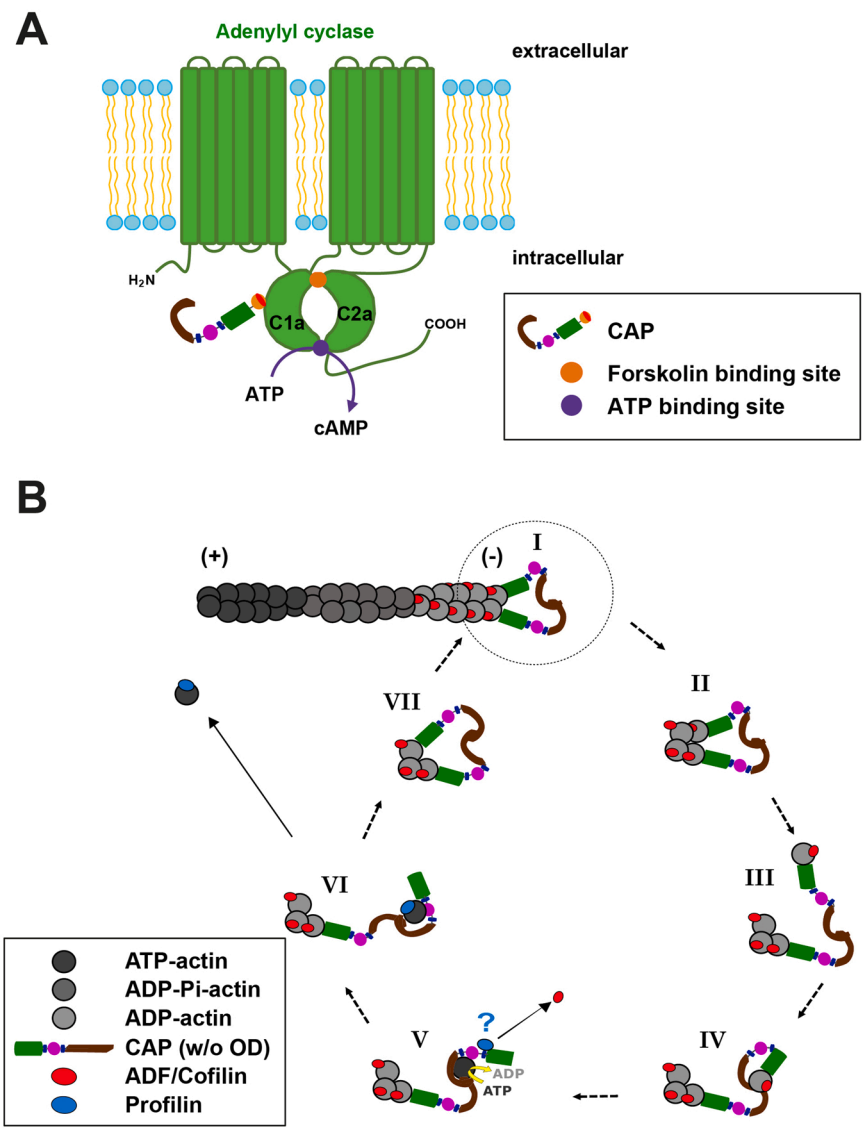

Fig. 2. CAP molecular functions. (A) RLE motifs within the N-terminal region of CAP are crucial for CAP's interaction with the catalytic loops (C1a and/or C2a) of the adenylate cyclase. This interaction can positively modulate cellular cAMP production and, hence, regulates intracellular signaling. (B) CAP from yeast to mammals accelerates various steps of the actin treadmilling mechanism including dissociation of actin subunits from F-actin in cooperation with ADF/cofilin as well as ATP for ADP exchange on G-actin needed for replenishing the pool of polymerization competent ATP-G-actin. For sake of simplicity, only the pointed (minus) end of F-actin (encircled in step I) is shown in the following steps. A detailed description of CAP function in cAMP signaling and actin dynamics is provided in the chapters 2.2 'CAP function in adenylyl cyclase regulation' and 2.3 'CAP functions in actin cytoskeleton regulation'.

2.2. CAP functions in actin cytoskeleton regulation

While a regulatory role in adenylyl cyclase activity and cAMP signaling has been unraveled only recently in mammals, very similar functions for yeast and mammalian CAP orthologs in actin cytoskeleton regulating have been established by studies of the past decade (Johnston et al., 2015; Kotila et al., 2018, 2019; Rust et al., 2020; Schneider et al., 2021a; Shekhar et al., 2019). From these studies it became evident that CAP contains several protein domains capable of binding actin, albeit with different affinities and preferences for adenosine diphosphate (ADP)-actin versus adenosine triphosphate (ATP)-actin, and that these domains are crucially important for different steps of the actin treadmilling mechanism. In this paragraph, for sake of better readability, we will mostly not differentiate between orthologs from different species, and we will use the term CAP for all orthologs investigated. In a current model of actin regulation (Fig. 2B), CAP's HFD interacts with ADF/cofilin-decorated pointed (minus) ends of F-actin consisting of ADP-actin, and it thereby accelerates dissociation of actin subunits (Kotila et al., 2019; Quintero-Monzon et al., 2009; Chaudhry et al., 2013; Shekhar et al., 2019). A recent genetic approach in primary mouse hippocampal neurons not only confirmed the interaction of CAP with ADF/cofilin, but also showed mutual functional dependence of both ABP in actin cytoskeleton regulation (Schneider et al., 2021a). Upon dissociation from F-actin, G-actin is transferred to the CARP domain that has a high affinity for ADP-G-actin and that, presumably together with the WH2 domain, weakens the interaction of ADP-G-actin with HFD as well as with ADF homology (ADF-H) domain, the actin-binding domain of ADF/cofilin (Balcer et al., 2003; Chaudhry et al., 2014, 2010; Kotila et al., 2018; Makkonen et al., 2013; Mattila et al., 2004; Moriyama and Yahara, 2002). Consequently, HFD as well as ADF/cofilin dissociate from ADP-G-actin, and the CARP domain in cooperation with the WH2 domain accelerates ATP-for-ADP exchange on G-actin (Chaudhry et al., 2014, 2010; Jansen et al., 2014; Kotila et al., 2018; Quintero-Monzon et al., 2009). Subsequently, ATP-G-actin is either released to the surrounding or transferred to ABP with high affinity for ATP-G-actin such as profilin (Bertling et al., 2007; Makkonen et al., 2013). Hence, CAP controls both actin subunit dissociation and replenishing the pool of polymerization-competent ATP-G-actin, making it an essential regulator of the actin treadmilling mechanisms.

Further, functional interaction of CAP with several established actin regulators apart from ADF/cofilin, including twinfilin, profilin, INF2 or ABP1 have been demonstrated. These interactions likely contribute to its function in actin regulation in vivo, though experimental evidences for some of them are still missing (Ono, 2013; Rust et al., 2020). Twinfilin has been associated with lymphoma progression or cancer cell invasion (Meacham et al., 2009; Bockhorn et al., 2013), and it controls length of

cochlear stereocilia (Peng et al., 2009), which is important for hearing (McGrath et al., 2017). Twinfilin possesses two ADF-H domains allowing actin binding, and it has been shown to sequester G-actin and to control actin turnover at filaments' barbed ends (Goode et al., 1998; Vartiainen et al., 2000; Ojala et al., 2002; Hakala et al., 2021; Shekhar et al., 2021). Further, yeast twinfilin strongly accelerated pointed end depolymerization in concert with CAP (Johnston et al., 2015), but this cooperation is not conserved in mammals (Hilton et al., 2018). Moreover, sophisticated total internal reflections fluorescence (TIRF) microscopy studies on single filaments elucidated twinfilin's functions at barbed ends, which were independent of CAP (Hakala et al., 2021; Shekhar et al., 2021).

Profilin promotes F-actin assembly by delivering ATP-G-actin to actin nucleating and/or polymerizing proteins such as formins, enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) proteins or the actin-related protein 2/3 (Arp2/3) complex (Ferron et al., 2007; Funk et al., 2019; Paul and Pollard, 2008; Rust et al., 2012; Skruber et al., 2020). Yeast profilin can interact with CAP's P1 both in vitro and in vivo, while mouse profilin interacts with both proline-rich motifs (Bertling et al., 2007; Makkonen et al., 2013). Apart from profilin, P1 is capable of interacting with Src homology 3 (SH3) domains e.g. from ABP1 or the tyrosine kinase abelson murine leukemia viral oncogene homolog (ABL), and yeast studies showed that the interaction with ABP1 controls the localization of CAP in cortical actin-rich structures (Balcer et al., 2003; Freeman et al., 1996; Lila and Drubin, 1997). However, the functional relevance of the interaction with profilin or ABP1 remains elusive, because P1 mutations induced only mild defects in yeast and because a CAP1 variants with mutated P1 fully rescued morphological changes in hippocampal neurons from brain-specific CAP1-KO mice, unlike CAP1 variants with mutated HFD or CARP domain (Bertling et al., 2007; Schneider et al., 2021a). Nevertheless, a genetic approach in *D. melanogaster* suggested functional interaction of CAP with ABL in axonal pathfinding (Wills et al., 2002).

More recently, both mammalian CAPs have been identified as components of a protein complex that inhibits the F-actin assembly factor INF2 (A et al., 2020, 2019). These studies revealed that CAP forms a complex with lysine-acetylated (KAc) actin (CAP/KAc-actin) that binds two regulatory domains of INF2, i.e., DID (Diaphanous inhibitory domain) and DAD (Diaphanous autoregulatory domain) (A et al., 2020, 2019). Thereby, CAP/KAc-actin forms a bridge between both regulatory domains, which keeps INF2 in an inactive state - a mechanism that has been termed 'facilitated autoinhibition' (A et al., 2019). Interestingly, dominant missense mutations in these regulatory domains have been associated with the kidney disease focal segmental glomerulosclerosis (FSGS) as well as the peripheral neuropathy CMTD (Boyer et al., 2011; Brown et al., 2010). Since these disease-associated mutants were only poorly inhibited by CAP/KAc-actin complexes, it has been speculated that impaired CAP/KAc-actin-mediated INF2 inhibition cause or contribute to FSGS as well as CMTD (A et al., 2019). Together, CAP not only controls actin dynamics by accelerating pointed end actin dissociation and G-actin recycling, but also by modulating the activity of established actin regulators, thereby further highlighting its relevance for actin cytoskeleton regulation.

3. Physiological functions

3.1. Heart

3.1.1. Heart defects in CAP2-KO mice

Analyses of a systemic knockout (KO) mouse model provided by the European Conditional Mouse Mutagenesis Program (EUCOMM) led to important novel insights into the physiological functions of CAP2. An initial study reported severe cardiac defects in CAP2-KO mice that were mainly characterized by a reduced heart rate (bradycardia), prolonged atrial and ventricular conductions times and a dilated cardiomyopathy (DCM) (Peche et al., 2012), which is a leading cause of heart failure in humans (Hershberger et al., 2013). Cardiac defects were likely causative for increased mortality of CAP2-KO mice that mostly died from sudden cardiac death (SCD). Interestingly, DCM and SCD were both more pronounced among male CAP2-KO mice reminding of human patients hospitalized for acute heart failure for which gender-related differences in clinical phenotypes have been reported (Nieminen et al., 2008). Subsequent studies confirmed cardiac defects in CAP2-KO mice, and they provided deeper mechanistic insights (Field et al., 2015; Stockigt et al., 2016; Xiong et al., 2019). Long-term electrocardiogram (ECG) recordings confirmed bradycardia in CAP2-KO mice, and they revealed spontaneous ventricular arrythmias, prolonged PQ and QT intervals as well as higher susceptibility to malignant ventricular arrhythmias (tachycardias) (Stockigt et al., 2016). Cardiac defects including impaired conduction, DCM and SCD were also reported for a second systemic CAP2-KO strain, again with higher incidence in males (Field et al., 2015). Moreover, by exploiting conditional KO mice, this study proved that CAP2 inactivation in cardiomyocytes caused cardiac defects and SCD. Transcriptome analysis of both CAP2-KO hearts and cardiomyocytes revealed an upregulation of genes controlled by the transcription factor serum response factor (SRF) prior to the onset of cardiac defects (Xiong et al., 2019). SRF is crucial for both heart development and maintenance of cardiac homeostasis, and its genetic inactivation as well as its overexpression in mice caused DCM (Dirkx et al., 2013; Parlakian et al., 2005, 2004; Zhang et al., 2001), suggesting that SRF dysregulation contributed to heart pathology in CAP2-KO mice. Indeed, systemic administration of the SRF inhibitor CCG-1423-8u not only reduced expression of SRF target genes, but also prolonged survival of CAP2-KO mice and restored cardiac structure and function to some extent (Xiong et al., 2019). Mechanistically, CAP2 inactivation may cause SRF dysregulation and, hence, cardiac defects via an actin-dependent mechanism. SRF activity is controlled by two classes of co-activators, members of either the ternary complex factor (TCF) family or the myocardin-related transcription factor (MRTF) family, which both compete for SRF binding and dictate specific gene repertoires (Olson and Nordheim, 2010; Onuh and Qiu, 2020). MRTF is an ABP that specifically binds G-actin, and G-actin-binding in turn inhibits MRTF-SRF interaction. Hence, MRTF-SRF-dependent gene expression is induced by a decline in G-actin levels, and ABP that control the balance between F- and G-actin such as CAP2 are very good candidates to act upstream of the MRTF-SRF pathway. Indeed, a recent study established CAP2 as a regulator of MRTF-SRF-dependent gene expression in mouse embryonic fibroblasts (Kepser et al., 2021). Taken together, CAP2-KO mice displayed a severe heart pathology characterized by impaired cardiac conduction, bradycardia, spontaneous arrhythmias and DCM, which together culminated in SCD. This phenotype was associated with aberrant sarcomere organization and reduced cooperativity of Ca^{2+}-induced force generation (Peche et al., 2012), which both likely contributed to the pathology.

3.1.2. CAP2 mutations associated with human cardiomyopathies

Based on the aforementioned studies that identified CAP2 as a crucial regulator of cardiac function in mice, it has been postulated that mutations in the human CAP2 gene can cause cardiomyopathies as well (Ono, 2013; Peche et al., 2012; Stockigt et al., 2016). Indeed, a genetic study identified a nucleotide exchange in the donor splice consensus sequence of exon 7 (c636 +1 G>A) in human CAP2 gene as the causative mutation in two consanguineous children with DCM and cardiac conduction impairments (Aspit et al., 2019). This nucleotide exchange caused an 'in frame' deletion of exon 6 and 7, thereby resulting in a protein that lacked 64 amino acids of the HFD and is very likely compromised in actin cytoskeleton regulation (see chapter 2.2 CAP functions in actin cytoskeleton regulation). Subsequently, dilated ventricles associated with functional tricuspid and pulmonary atresia as well as impaired systolic function have been diagnosed in a fetus with homozygous CAP2 mutation at 30 weeks of gestation (Patel and Peterson, 2019). Unfortunately, the pathogenic CAP2 variant in this patient

was not specified. However, the report noted that both not-affected consanguineous parents were heterozygous for the same variant and that this couple had a previous infant that died at the age of four months with very similar cardiac defects. The earlier onset and more severe cardiac phenotype in this patient compared to those described by Aspit and colleagues could be caused by higher pathogenicity of the CAP2 mutation. Alternatively, additional heterozygous variants of the DCM susceptible genes TCAP and/or MYH7, which encode the sarcomere protein telethonin and myosin heavy chain 7, respectively, have been reported in this patient and these variants may act as disease amplifiers (Wadmore et al., 2021; Yotti et al., 2019). Severe early onset DCM has been additionally linked to a homozygous nonsense mutation at Y316 of CAP2 in a screen of a large cohort with suspected genetic diseases, which aimed at establishing exome sequencing as a diagnostic tool to achieve genetic diagnosis (Cheema et al., 2020). Finally, a homozygous frame shift mutation (c430fs), which caused loss of CAP2 protein, has been associated with DCM and ventricular dysfunction in a male infant just recently (Gurunathan et al., 2021). Importantly, this study not only confirmed an association of CAP2 loss-of-function with DCM and cardiac dysfunction in humans, but also with skeletal muscle defects (see chapter 3.2.2 CAP2 mutation associated with human myopathy). Interestingly, the National Heart, Lung and Blood Institute's TOPMed program identified 19 distinct CAP2 loss-of-function mutations including 10 individuals with the c430fs variant, making this mutation the most common pathogenic CAP2 variant (Taliun et al., 2021). However, all of these individuals were heterozygous carriers without any associated clinical findings. Together, human genetic studies of the past years identified various pathogenic CAP2 variants, which were all associated with neonatal or infantile onset DCM and cardiac defects. These defects emerged as the predominant human phenotype upon CAP2 loss-of-function, thereby reflecting the findings in CAP2-KO mice. However, a more comprehensive and in-depth analysis of both CAP2-KO mice and human patients revealed additionally defects in skeletal muscles.

3.2. Skeletal muscle

3.2.1. Myopathy in CAP2-KO mice and CAP2 functions in actin cytoskeleton differentiation during striated muscle development

CAP2 is not only abundant in the heart, but also in skeletal muscles (Bertling et al., 2004; Peche et al., 2007). However, its function in the latter has been unraveled only recently, again by exploiting systemic CAP2-KO mice from EUCOMM. In skeletal muscle, CAP2 controls the sequential exchange of α-actin isoforms from smooth muscle and cardiac to skeletal muscle α-actin (Kepser et al., 2019). This 'α-actin switch' occurs in mice during early postnatal development and is a crucial step during myofibril differentiation (Tondeleir et al., 2009). Consequently, CAP2 inactivation did not impair embryonic myogenesis, but delayed postnatal myofibril differentiation that disturbed skeletal muscle architecture. The CAP2-KO myopathy was mainly characterized by a frequent occurrence of ring fibers, and it affected mutant mice of either sexes equally, unlike the cardiomyopathy (Kepser et al., 2019). Ring fibers are myofibers containing displaced myofibrils with a perpendicular orientation to the main group of longitudinally orientated myofibrils (Banker and Engel, 1986; Carpenter and Karpati, 1984), and they have been reported not only for human myopathies such as nemaline myopathy, myotonic dystrophy, limb-girdle dystrophy or inclusion body myositis, but also for congenital human myopathies of unknown etiology (Bethlem and Vanwijngaarden, 1963; Del Bigio and Jay, 1992; Joyce et al., 2012). A similar ring fiber pathology has been reported in mutant mice expressing a pathogenic variant of ACTA1 encoding skeletal muscle α-actin, which has been associated with severe myopathy in humans (Agrawal et al., 2004; Ravenscroft et al., 2011). Apart from displaced myofibrils, CAP2-KO myofibers frequently contained internalized nuclei as well as dislocated mitochondria (Kepser et al., 2019). Histopathological features in CAP2-KO mice coincided with the onset of motor function deficits. Specifically, neonatal CAP2-KO mice of either sex displayed a delay in motor function development, while visual, auditory and tactile perception as well as reflexes developed normally. Moreover, muscle strength was moderately reduced in juvenile and adult CAP2-KO mice, suggesting that CAP2 inactivation impaired motor function throughout lifetime (Kepser et al., 2019). Together, this study identified CAP2 as a crucial regulator of actin cytoskeleton differentiation that is required for proper skeletal muscle development and function.

Notably, a more recent study unraveled a very similar function for CAP2 in cardiomyocytes (Colpan et al., 2021). This study showed that CAP2 controls actin depolymerization from filaments' pointed ends, which is crucial for the exchange of α-actin isoforms from smooth muscle and skeletal muscle to cardiac α-actin during cardiomyocyte differentiation. In cardiomyocytes, CAP2-mediated actin cytoskeleton differentiation precedes - and presumably is a prerequisite for – the function of tropomodulin (Tmod) and leiomodin (Lmod) (Iwanski et al., 2021). These two ABPs act as competing factors at filaments' pointed ends and synergistically control filaments' length, and they thereby affect sarcomere organization and cardiac function (Fowler and Dominguez, 2017). Inactivation of these factors in mice compromised heart development and caused DCM, phenotypes that were mirrored in human patients expressing pathogenic variants (Ahrens-Nicklas et al., 2019; Fowler and Dominguez, 2017; Pappas et al., 2015). Hence, impaired myofibril differentiation in cardiomyocytes likely contributes to sarcomere disorganization and to compromised cardiac function in CAP2-KO mice. Together, CAP2 emerged as a critical regulator for fine tuning the actin cytoskeleton in myocytes as well as cardiomyocytes, and defects in actin cytoskeleton differentiation caused or contribute to skeletal muscle and heart phenotypes in CAP2-KO mice. The delay in the 'α-actin switch' in CAP2-KO striated muscles not only altered the actin composition in thin filaments, but also the abundance of actin isoforms among G-actin (Kepser et al., 2019). Future studies will show whether the latter contributes to altered MRTF-SRF-dependent gene expression in striated muscles from CAP2-KO mice.

Very similar to CAP2-KO mice, a delayed 'α-actin switch' during skeletal muscle has been reported for mutant mice lacking cofilin2 (Gurniak et al., 2014), the ADF/cofilin family member enriched in striated muscles (Thirion et al., 2001). Based on this finding and supported by phenotype similarities in mutant mouse strains (Agrawal et al., 2012; Gurniak et al., 2014; Kepser et al., 2019), a cooperation of CAP2 and cofilin2 in actin cytoskeleton differentiation during skeletal muscle development has been proposed (Kepser et al., 2019; Rust et al., 2020). Such a cooperation is not only in very good agreement with the above outlined molecular CAP functions (see Section 2.2 CAP functions in actin cytoskeleton regulation), but also with an earlier study that suggested an interaction of the CAP2 and cofilin2 orthologs CAS-1 and UNC-60B, respectively, during striated muscle development in *C. elegans* (Nomura et al., 2012). Although cofilin2-KO mice and CAP2-KO mice displayed similarities in the onset and progression of their myopathies, cofilin2-KO mice were not viable and died within two weeks after birth, thereby preventing phenotype comparisons at later stages. However, a previous study implicated cofilin2 in regulating actin depolymerization from filaments' pointed ends in cardiomyocytes (Kremneva et al., 2014), similar to the CAP2 function outlined above (Colpan et al., 2021). It is therefore very well conceivable that CAP2 and cofilin2 cooperate in actin cytoskeleton differentiation not only in skeletal muscles, but also in cardiomyocytes (Iwanski et al., 2021).

3.2.2. CAP2 mutation associated with human myopathy

While several human genetic studies associated pathogenic CAP2 variants with DCM and cardiac dysfunction (Aspit et al., 2019; Cheema et al., 2020; Patel and Peterson, 2019), skeletal muscle defects have been reported just recently (Gurunathan et al., 2021). The reason for this could be that loss-of-function mutations in human CAP2 induced a quite severe heart pathology with prenatal or early postnatal onset (Aspit

et al., 2019; Cheema et al., 2020; Patel and Peterson, 2019), but may only mildly affect motor functions, similar to CAP2 mutant mice (Field et al., 2015; Kepser et al., 2019; Peche et al., 2012; Stockigt et al., 2016). Consequently, motor dysfunction may have been overlooked by clinicians in human patients. Exemplarily, the first two human patients with CAP2 mutations were diagnosed for DCM and cardiac conduction defects at the ages of 5 and 12 years, respectively (Aspit et al., 2019). The older patient died shortly after diagnosis before complete phenotype characterization, and the younger patient was on amiodarone therapy that is notoriously associated with adverse side effects including muscle weakness (Besser et al., 1994). Nevertheless, a recent study associated CAP2 (c430fs) loss-of-function mutation not only with DCM and cardiac dysfunction, but also with nemaline myopathy and a delay in motor function (Gurunathan et al., 2021). Nemaline myopathy is a skeletal muscles disorder that - in the vast majority of cases - is caused by mutations in sarcomere proteins and that is characterized by an accumulation of microscopic rod or thread-like structures (nemaline bodies). It is a heterogenous myopathy with an incidence of roughly 1 in 50,000 births, and it can be present in early childhood with muscle weakness, hypotonia as well as delayed development of motor function (Conen et al., 1963; de Winter and Ottenheijm, 2017; Shy et al., 1963). Interestingly, mutations in the human cofilin2 gene CFL2 are among the most common mutations in nemaline myopathy (Agrawal et al., 2007; Fattori et al., 2018; Finsterer and Stollberger, 2015; Ockeloen et al., 2012), and nemaline myopathy was present in both cofilin2-KO mice as well as in mutant mice expressing a pathogenic human CFL2 variant (Agrawal et al., 2012; Rosen et al., 2020), again supporting the notion of an intimate interaction of CAP2 and cofilin2 in myocytes. Together, a first human genetic study implicated a pathogenic CAP2 variant not only in heart pathology, but also in nemaline myopathy.

3.3. Nervous system

Different from most other tissues in vertebrates, CAP1 and CAP2 are both expressed in the nervous system. Exemplarily, northern blot and immunoblot analysis showed that CAP1 and CAP2 are both broadly expressed during brain development in mice (Bertling et al., 2004; Schneider et al., 2021c). *In situ* hybridization analysis revealed strong CAP1 expression in differentiated neurons of both central and peripheral nervous system at embryonic day (E) 14.5 and E18.5. Apart from muscle tissue, CAP2 expression was strong in the thalamic area of E18.5 brains, and weaker CAP2 expression was present in some peripheral ganglia (Bertling et al., 2004). In adult mouse brain, strongest expression of CAP1 and CAP2 was observed in the cortex and hippocampus (Bertling et al., 2004; Schneider et al., 2021a). The high levels of CAP expression in the nervous system mirrors their importance in specific processes involved in neuronal development, maintenance and function, which depend on the tight regulation of cytoskeleton organization and dynamics.

3.3.1. CAP functions during central nervous system development

The relevance of CAP1 in specific brain developmental processes emerged from the analysis of brain-specific CAP1-KO mice (Schneider et al., 2021a). CAP1 was dispensable for various important aspects of brain development such as neural stem cell proliferation and differentiation, neuron production and migration or layer formation in the cerebral cortex. However, CAP1-KO mice displayed slight changes in hippocampal morphology as well as compromised neuron connectivity, which could be ascribed to impaired neuron differentiation (Schneider et al., 2021a). Neuron connectivity depends on growth cones that navigate axons through the developing brain. The peripheral domain of growth cones is highly enriched in dynamic F-actin and contains receptors that translate guidance cues into intracellular signaling activities that act upstream of ABP to control F-actin assembly and disassembly. The accurate navigation of neuronal growth cones through the embryonic brain is essential for the formation of a functional neuronal network (Leite et al., 2021). The involvement of CAP in axon guidance initially emerged from studies performed in *D. melanogaster*. As reported above (see chapter 2.2 CAP functions in actin cytoskeleton regulation), studies of embryonic axon guidance suggested that ABL collaborates with the CAP ortholog in *D. melanogaster* named Capulet or Act up in the accurate navigation of developing axons. These studies further suggested that Capulet/Act up is part of a pathway that links guidance signals to the regulation of cytoskeletal dynamics (Wills et al., 2002).

The analysis of hippocampal neurons isolated from brain-specific CAP1-KO mice demonstrated the importance of CAP1 for growth cone function (Schneider et al., 2021a). CAP1-KO neurons displayed defects in growth cones size, morphology and motility as well as an impaired response to attractant and repellant guidance cues. CAP1 is located in growth cones, and growth cone morphological changes in CAP1-KO neurons were associated with impaired actin turnover and F-actin dynamics. From a mechanistic point of view, rescue experiments in CAP1-KO neurons and the analysis of neurons lacking CAP1 and cofilin1, a key actin regulator which has been implicated in growth cone actin dynamics (Omotade et al., 2017; Schneider et al., 2021b), revealed functional interdependence and cooperation of both ABP in growth cones (Schneider et al., 2021a), in good agreement with their molecular functions (see Section 2.2).

Very similar to CAP1, CAP2 is present during neuron differentiation and abundant in growth cones. However, analysis in CAP2-KO neurons revealed that CAP2 was not critical for neuron differentiation, and that it was dispensable for growth cone morphology and motility (Schneider et al., 2021c). Accordingly, systemic CAP2-KO mice did not display any gross defects in brain development. Interestingly, rescue experiments in CAP1-KO neurons revealed redundant functions for CAP1 and CAP2 in differentiating neurons. Specifically, CAP2 overexpression rescued neuron differentiation as well as neurite width and total neurite length changes in CAP1-KO neurons, and it partially rescued growth cone size (Schneider et al., 2021c). Functional redundancy of mouse CAP1 and CAP2 has been postulated earlier (Field et al., 2015), and this study proved overlapping functions for CAP1 and CAP2 in differentiating neurons.

3.3.2. CAP functions in the developed brain

While CAP2 was dispensable during neuron differentiation, it controls the morphology of dendritic spines in differentiated neurons. Dendritic spines are postsynaptic structures of the vast majority of excitatory synapses in the vertebrate brain that integrate synaptic input. These structures are highly enriched in F-actin and can change their morphology in response to neuronal activity. Structural plasticity of dendritic spines is tightly coordinated with synaptic function, and it is controlled by ABP that modify the postsynaptic actin cytoskeleton and, hence, confer spine plasticity and stability (Cingolani and Goda, 2008; Hotulainen and Hoogenraad, 2010; Pelucchi et al., 2020a). Consequently, dysregulation of the dendritic spine actin cytoskeleton alters spine morphology and it impairs synaptic plasticity, brain function and ultimately behavior. It has been shown that CAP2 is specifically located in dendritic spines regions enriched in F-actin (Pelucchi et al., 2020b). Remarkably, CAP2 inactivation differently affected neuron structure and dendritic spine morphology in cortical and hippocampal neurons. Primary cortical neurons from CAP2-KO mice displayed an increase in dendrite complexity and spine density (Kumar et al., 2016), whereas CAP2 downregulation in primary hippocampal neurons reduces dendritic arborization along with a significant increase in spine length and head width (Pelucchi et al., 2020b). Structural alterations in hippocampal neurons were accompanied by defects in synaptic transmission and plasticity, highlighting the relevance of CAP2 for synapse physiology and neuronal function. The mechanism underlying such effect involved cofilin1. It has been shown that CAP2 forms dimers through its Cys32 and that dimerization was important for both cofilin1 binding and actin turnover. Long-term potentiation (LTP) of synaptic transmission triggers cofilin1 translocation into spines where its activity was required

for the rapid sculpturing of the actin cytoskeleton and, hence, for spine morphological changes (Bosch et al., 2014). Relevance of cofilin1 for spine morphology and synaptic plasticity has been proven by the analyses of gene-targeted mice lacking either cofilin1 or cofilin1 and its close homolog ADF (Rust, 2015; Rust et al., 2010; Wolf et al., 2015), and synaptic defects in these mutants were associated with altered behavior (Goodson et al., 2012; Rust and Maritzen, 2015; Sungur et al., 2018; Zimmermann et al., 2015). The Cys32-dependent dimerization of CAP2 is necessary for LTP-induced cofilin1 translocation into spines, spine remodeling and the potentiation of synaptic transmission (Pelucchi et al., 2020b), suggesting a crucial role for CAP2 in brain function and behavior, similar to cofilin1. Overall, these studies highlight that both CAP1 and CAP2 orchestrate neuronal actin cytoskeleton dynamics in close cooperation with cofilin1, in different subcellular compartments, such as dendritic spines and growth cones both during critical neurodevelopmental events such as axonal outgrowth and neuron differentiation, but also in differentiated neurons.

3.3.3. Potential contribution of CAP to brain disorders

Proper balance in the activity of cofilin1, the interaction partner of both CAP1 and CAP2 in the mouse brain, is a prerequisite for brain development and function, and cofilin1 dysregulation has been associated with various brain disorders (Bamburg et al., 2021; Namme et al., 2021). Recent studies have also reported alterations in the expression of CAPs or defects in CAP-regulated mechanisms associated to different brain diseases, ranging from neurodevelopmental to neurodegenerative disorders.

Schizophrenia has been conceptualized as a neurodevelopmental disorder affecting synaptic plasticity and cortical-subcortical connectome (Lewis and Levitt, 2002; Murray et al., 2017). It is a polygenic and multifactorial disorder and several genetic studies aimed at identifying candidate genes relevant for the etiology or pathophysiology. Analysis of differential gene transcription patterns in a schizophrenia animal model revealed altered CAP1 expression in the temporal cortex (Wong et al., 2005). In support of a CAP1 involvement in schizophrenia, increased CAP1 protein levels have been found in the mediodorsal thalamus of schizophrenia patients (Martins-de-Souza et al., 2010). On the other hand, CAP2 mRNA levels wear reduced in the hippocampus, but not in the dorsolateral prefrontal cortex of schizophrenia patients compared to non-psychiatric control subjects (Di Maio et al., 2022). Even though no differences were detected at protein level, these data suggest that an aberrant expression of CAP2 in the hippocampus can be associated to schizophrenia. In addition, a linkage and exome study reported a rare variant residing in the 5'-UTR of the CAP2 gene, which has been implicated in the pathogenesis of bipolar disorder, a severe and complex psychiatric condition characterized by alternating episodes of depression and mania (Anjanappa et al., 2020).

Alterations in CAP1 expression have been observed in the cortex of animal models for neuronal ceroid lipofuscinoses, which are a group of children inherited neurodegenerative disorders characterized by blindness, early dementia and pronounced cortical atrophy (von Schantz et al., 2008). Transcript profile analysis pointed to potential impairment of genes related to cytoskeleton-mediated growth cone. Indeed, cortical neurons from animal models of this disease revealed growth cone abnormalities (von Schantz et al., 2008). These data are in line with a crucial role of CAP1 in regulation growth cone actin dynamics (Schneider et al., 2021a), highlighting the importance of CAP1 for neuron differentiation. Instead, CAP2 levels and synaptic localization are specifically reduced in the hippocampus, but not in the cortex of Alzheimer's Disease patients (Pelucchi et al., 2020b). In addition, in hippocampal synapses of these patients, CAP2 dimer levels are reduced and an aberrant association of cofilin1 to CAP2 covalent dimer/monomer has been reported (Pelucchi et al., 2020b). These data suggest that the CAP2-cofilin1 complex is impaired in Alzheimer's Disease hippocampal synapses, which may contribute to structural plasticity defects in such form of dementia. In summary, CAP1 and CAP2 emerged as important regulators of mammalian brain development and function, and their dysregulation likely cause or contribute to the pathologies of various brain disorders.

3.4. Metabolic functions

3.4.1. Potential contribution of CAP to metabolic diseases

Obesity is associated with a high incidence of well-known cardiovascular risk factors such as dyslipidemia, hypertension and diabetes. Numerous studies have shown the existence of a cardiovascular continuum, in which pathological processes begin as the result of various risk factors and lead to permanent changes and cardiovascular complications through endothelial damage, vascular and myocardial remodeling, and atherosclerotic processes (Drozdz et al., 2021). Interestingly, both CAP1 and CAP2 were modulated by high-fat diet consumption (Lee et al., 2014), and CAP1 participated in pathways implicated in increased risk of cardiovascular disease such as inflammation and cholesterol homeostasis. For instance, the administration of high-fat diet affected CAP2 phosphorylation in the muscle. Obesity can also lead to ectopic lipid accumulation in skeletal muscle and is associated with muscle weakness and insulin resistance (Consitt et al., 2009; Kaneko et al., 2011; Kemp et al., 2009; Ritov et al., 2010). Phospho-proteome analysis of skeletal muscle revealed that high-fat diet inhibited the phosphorylation of CAP2 at Ser196 and Ser199. Considering the crucial role of CAP2 in skeletal muscle (see chapter 3.2.1 Myopathy in CAP2-KO mice and CAP2 functions in actin cytoskeleton differentiation during striated muscle development), changes in its phosphorylation may contribute to muscular atrophy induced by high-fat diet (Sun et al., 2020). On the other hand, CAP1 has been reported as adipopkine receptor (Lee et al., 2014) and binding partner of proprotein convertase subtilisin/kexin type-9 (PCSK9) (Jang et al., 2019), thus suggesting novel biological functions going beyond actin cytoskeleton remodeling. CAP1 emerged as a critical regulator of metabolic function, that may control inflammatory processes as well as lipoprotein metabolism via its interaction with resistin and PCSK9, as described in the following chapters.

3.4.2. CAP1 acts a receptor of the cytokine resistin

CAP1 may play a pivotal role in atherosclerosis processes because it has been described as the functional receptor for human resistin (Lee et al., 2014), a mediator of obesity-related insulin resistance. Resistin is a pro-inflammatory adipokine that promotes recruitment of immune cells and secretion of proinflammatory factors (Bokarewa et al., 2005; Silswal et al., 2005), correlated with fat mass and acting on endothelial dysfunction and cardiovascular diseases (Musovic et al., 2021). Increasing evidence linked resistin with inflammation and atherogenesis (Burnett et al., 2005; Jung et al., 2006; Reilly et al., 2005). Indeed, atherosclerosis can be considered as an inflammatory disorder characterized by the retention of modified low-density lipoproteins (LDL) in the arterial wall, a burden initiated by the intramural retention of atherogenic lipoproteins, activating resident macrophages and recruitment of monocyte-derived cells. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes (Hansson, 2005).

Different putative receptors of resistin have been described, but showed rather very weak pro-inflammatory effect in humans, while CAP1 has been shown to mediate resistin-dependent inflammatory actions of human monocytes (Lee et al., 2014). CAP1 has been localized in the cytosol and in the membrane fraction of human monocytes. Exogenously applied resistin elicited a change in CAP1 localization to the membrane surface. Resistin and its receptor CAP1 increased intracellular cAMP concentration, PKA activity, and NF-κB-related transcription of many inflammatory cytokines in human monocytes. Furthermore, chemotaxis of macrophages or monocytes to resistin was dependent upon CAP1 (Lee et al., 2014). Human resistin binds to CAP1 via the proline-rich SH3-binding domain while the N-terminal domain likely

plays a key role in receptor signaling. Specifically, point mutations of Val27 and Ser28 in CAP1-SH3 binding domain (corresponding to Val242 and Ser243 of full-length human CAP1) abolished interaction between resistin and CAP1. On the other hand, the actin binding domain of CAP1 might have a pivotal role on the resistin-related migration activity of human monocytes (Lee et al., 2014). Following a 1-month period of a high-fat diet, CAP1 expression was increased in the white adipose tissue of humanized resistin mice along with resistin. Remarkably, CAP1-overexpressing monocytes aggravated adipose tissue inflammation in such transgenic mice. In contrast, suppression of CAP1 expression abrogated the resistin-mediated inflammatory activity (Lee et al., 2014). In this context, CAP1 represents a suitable pharmacological target to counteract resistin-triggered inflammation. For instance, celastrol, a pentacyclic triterpene compound derived from the roots of the *Tripterygium wilfordii*, binds CAP1 and reduces interaction between resistin and CAP1, thus preventing the subsequent inflammatory response. In line with these results, knockdown of CAP1 in macrophages abrogated the resistin-mediated inflammatory activity while CAP1 overexpression had an opposite effect. Remarkably, celastrol administration protects mice from high-fat diet-induced metabolic syndrome, since it reduced body weight, ameliorated insulin resistance and hepatic steatosis as well as attenuated inflammation (Zhu et al., 2021). Even though several biochemical binding assays have demonstrated the direct interaction between CAP1 and resistin and defined CAP1 as resistin receptor (Lee et al., 2014; Zhu et al., 2021), CAP1 lacks a transmembrane domain and should bind resistin in the cytoplasm. Further studies addressing how CAP1 is associated to the membrane are necessary to fully elucidate CAP1 cellular function.

3.4.3. CAP1 and proprotein convertase subtilisin/kexin type-9 (PCSK9)

In addition to the role in the inflammatory response, CAP1 may contribute to the pathogenesis of cardiovascular diseases as a novel binding partner of the proprotein convertase subtilisin/kexin type-9 (PCSK9) (Jang et al., 2019), a key player of plasma cholesterol homeostasis (Abifadel et al., 2003). Secreted PCSK9 binds to the LDL receptor (LDLR) at the hepatocyte cell surface and promotes its endocytosis and lysosomal degradation. Therefore, PCSK9 inhibition has been established as an approach for the treatment of hypercholesterolemia (Macchi et al., 2021). It has been shown that the SH3-binding domain of CAP1, that mediates binding to resistin (Lee et al., 2014), interacts directly with the C-terminal cysteine-rich domain of PCSK9. Interestingly, two loss-of-function polymorphisms of PCSK9 C-terminal Cys-rich domain showed a defective interaction with CAP1, and CAP1 downregulation in cellular systems prevented PCSK9-mediated LDLR degradation (Jang et al., 2019). These data were confirmed in heterozygous CAP1-KO mice, which had higher LDLR levels. Further, high-fat diet fed heterozygous CAP1-KO mice had lower plasma total cholesterol and LDL cholesterol compared to wild-type mice (Jang et al., 2019). From a mechanistic point of view, CAP1 promoted PCSK9-induced LDLR endocytosis. PCSK9 promotes clathrin-dependent LDLR endocytosis, that does not lead to lysosomal degradation of LDLR. On the other hand, the binding of LDLR/PCSK9 complex with CAP1 drives LDLR/PCSK9 towards caveolin-dependent endocytosis. Then, caveolin-coated endosomes containing LDLR/PCSK9/CAP1 are targeted to lysosomes for degradation. CAP1 binds to caveolin-1 through its N-terminal region and may be involved in caveolin-dependent endocytosis. Hence, CAP1 plays a crucial role in the PCSK9-dependent mechanisms that control LDLR degradation and, thereby, the cholesterol homeostasis (Jang et al., 2019). Taken together, CAP1 emerged as a critical regulator of metabolic function, that may control inflammatory processes as well as lipoprotein metabolism via its interaction with resistin and PCSK9.

3.5. Potential contribution of CAP2 to 6p22 syndrome

6p22 syndrome is a rare developmental disorder defined by deletions in the distal part of the short arm of chromosome 6. The phenotype of 6p22 patients shows a large variability, but usually includes developmental delay, hypotonia, psychomotor retardation, craniofacial and limb malformations, heart and kidney defects as well as eye abnormalities (Davies et al., 1999). Phenotype variability in 6p22 patients is caused by different size and location of chromosomal deletions (i.e. terminal or proximal interstitial deletions). Two studies narrowed down the deletion region and identified a maximum overlapping region that includes 12 genes, among them *CAP2* (Bremer et al., 2009; Celestino-Soper et al., 2012), suggesting a contribution of CAP2 loss-of-function to 6p22 syndrome. However, it's difficult to ascribe pathological trait of 6p22 syndrome patients to the deletion of CAP2 gene. For instance, cardiac defects in 6p22 syndrome patients are different from the cardiomyopathy reported in CAP2-KO mice (Field et al., 2015) and in patients carrying pathogenic mutations in CAP2 gene (Aspit et al., 2019). In addition, CAP2-KO mice are not characterized by neurodevelopmental delay that is one of the main pathological features of 6p22 syndrome patients (Bremer et al., 2009; Celestino-Soper et al., 2012). In light of these considerations, further studies are required to clarify the role of the loss of CAP2 in determining the pathological phenotype of 6p22 patients.

4. Concluding remarks

CAP1 and CAP2 have been recognized as ABP capable of modulating subunit dissociation from F-actin and nucleotide exchange on G-actin. However, studies carried out in the last 20 years revealed the complexity of CAPs biology at the molecular and cellular level. At the molecular level, CAP1 and CAP2 are characterized by a similar structure constituted of different domains that cooperate to control the actin cytoskeleton. CAPs bind actin but they can also interact with other ABP to control their activity (Rust et al., 2020). Therefore, CAPs action on actin cytoskeleton dynamics can be dependent on the synergistic interaction with different ABPs. In the cells, CAPs biological role is not restricted to the control of actin cytoskeleton treadmilling, and CAPs have been implicated in signal transduction pathways. In the yeast, CAP has been discovered as binding partner of the adenylyl cyclase that suppresses a hyperactive RAS2 variant (Field et al., 1990). However, the role on cAMP signaling is conserved in mammals through Rap1. CAP1 is a geranylgeranyl-binding partner of Rap1 (Zhang et al., 2018) and modulates cAMP levels in a Rap1-dependent manner (Zhang et al., 2021). Considering that Rap1 is an established downstream effector of cAMP, CAP1-cyclase-Rap1 may represents a positive feedback loop implicated in local cAMP signaling (Zhang et al., 2021). More recently, CAP1 has been described as the cellular receptor of the adipokine resistin (Lee et al., 2014) and as a key regulator of LDLR levels (Jang et al., 2019). A tight interdependence of actin cytoskeleton and pathways controlling gene expression has been shown in different systems. In mouse embryonic fibroblasts, CAP2 has been shown as a regulator of gene expression through the MRTF-SRF pathway (Kepser et al., 2021). In *D. melanogaster* the loss of function of the CAP homolog (Capulet/Act up) alters the expression of key developmental genes, such as hedgehog and hippo, thus affecting the formation of the morphogenetic furrow in the eye imaginal disc (Benlali et al., 2000). Aberrant eye development has also been reported in CAP2-KO (Field et al., 2015). The mutant animals have microphthalmia characterized by reduced diameters of pupils in male CAP2-KO mice, which was associated to sensitivity to eye inflammation and infections. These studies positioned CAPs at the crossroads of different pathways and, thereby, uncovered the complexity of CAPs' roles at the cellular level.

Another level of complexity derives from the different expression patterns of CAP family members. CAP1 is expressed in almost all tissues except of skeletal muscle, while CAP2 is present in a limited number of tissues (Bertling et al., 2004). This observation suggests that CAP2 may have unique roles in specific tissues. The studies of CAP1-KO and CAP2-KO mice revealed the relevance of each member of the CAP family in the different tissues, especially during development. Functional

redundancy of mouse CAP1 and CAP2 has been postulated earlier (Field et al., 2015), but the analysis of the phenotype of the gene-targeted mice indicates that CAP1 is crucial for CNS development (Schneider et al., 2021a), while CAP2 is a key protein in skeletal muscles and heart (Peche et al., 2012; Field et al., 2015; Stockigt et al., 2016; Xiong et al., 2019; Kepser et al., 2019), in accordance with their expression profile. In other tissues CAP2 loss can be only partially recovered by CAP1. For instance, CAP2-KO mice show altered wound healing response and, even though CAP1 is upregulated in CAP2-KO unwounded skin and in wounds, it might partially compensate for the loss of CAP2 (Kosmas et al., 2015).

Recent human genetic studies and the analysis of gene-targeted mice highlighted the involvement of CAPs in several diseases. For instance, the global impact of the systemic loss of CAP2 has been revealed by genetic studies of patients affected by the 6p22 syndrome, a rare developmental disorder defined by deletions of the short arm of chromosome that includes CAP2 gene (Celestino-Soper et al., 2012; Bremer et al., 2009). However, in light of the comparison of the phenotype of patients with 6p22 syndrome and of subjects carrying CAP2 pathogenic variants, it is difficult to assign any phenotype to CAP2 loss in 6p22 syndrome.

Even though such studies contributed to our understanding of CAPs' physiological and pathological functions, there are still open questions in CAPs research field. How cellular signal transduction pathways control CAPs activity in the different cell types? Do CAP1 and CAP2 cooperate in the control of actin cytoskeleton dynamics? Further studies are required to address these issues and to add new pieces to the puzzle of CAPs cell biology.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by grants from the Cariplo Foundation (project code 2018- 0511) to MBR and EM, by a grant from the Deutsche Forschungsgemeinschaft (DFG) to MBR (RU 1232/7-1) and by grants to EM (Italian Ministry of University and Research (MIUR) PRIN 2017B9NCSX and PRIN 202039WMFP). MBR was supported by the DFG Research Training Group 'Membrane Plasticity in Tissue Development and Remodeling' (GRK 2213).

References

A, M., Fung, T.S., Kettenbach, A.N., Chakrabarti, R., Higgs, H.N., 2019. A complex containing lysine-acetylated actin inhibits the formin INF2. Nat. Cell Biol. 21, 592–602.

A, M., Fung, T.S., Francomacaro, L.M., Huynh, T., Kotila, T., Svindrych, Z., Higgs, H.N., 2020. Regulation of INF2-mediated actin polymerization through site-specific lysine acetylation of actin itself. Proc. Natl. Acad. Sci. USA 117, 439–447.

Abifadel, M., Varret, M., Rabes, J.P., Allard, D., Ouguerram, K., Devillers, M., Cruaud, C., Benjannet, S., Wickham, L., Erlich, D., Derre, A., Villeger, L., Farnier, M., Beucler, I., Bruckert, E., Chambaz, J., Chanu, B., Lecerf, J.M., Luc, G., Moulin, P., Weissenbach, J., Prat, A., Krempf, M., Junien, C., Seidah, N.G., Boileau, C., 2003. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat. Genet 34, 154–156.

Agrawal, P.B., Strickland, C.D., Midgett, C., Morales, A., Newburger, D.E., Poulos, M.A., Tomczak, K.K., Ryan, M.M., Iannaccone, S.T., Crawford, T.O., Laing, N.G., Beggs, A. H., 2004. Heterogeneity of nemaline myopathy cases with skeletal muscle alpha-actin gene mutations. Ann. Neurol. 56, 86–96.

Agrawal, P.B., Greenleaf, R.S., Tomczak, K.K., Lehtokari, V.L., Wallgren-Pettersson, C., Wallefeld, W., Laing, N.G., Darras, B.T., Maciver, S.K., Dormitzer, P.R., Beggs, A.H., 2007. Nemaline myopathy with minicores caused by mutation of the CFL2 gene encoding the skeletal muscle actin-binding protein, cofilin-2. Am. J. Hum. Genet. 80, 162–167.

Agrawal, P.B., Joshi, M., Savic, T., Chen, Z., Beggs, A.H., 2012. Normal myofibrillar development followed by progressive sarcomeric disruption with actin accumulations in a mouse Cfl2 knockout demonstrates requirement of cofilin-2 for muscle maintenance. Hum. Mol. Genet. 21, 2341–2356.

Ahrens-Nicklas, R.C., Pappas, C.T., Farman, G.P., Mayfield, R.M., Larrinaga, T.M., Medne, L., Ritter, A., Krantz, I.D., Murali, C., Lin, K.Y., Berger, J.H., Yum, S.W., Carreon, C.K., Gregorio, C.C., 2019. Disruption of cardiac thin filament assembly arising from a mutation in LMOD2: A novel mechanism of neonatal dilated cardiomyopathy. Sci. Adv. 5, eaax2066.

Anjanappa, R.M., Nayak, S., Moily, N.S., Manduva, V., Nadella, R.K., Viswanath, B., Reddy, Y.C.J., Jain, S., Anand, A., 2020. A linkage and exome study implicates rare variants of KANK4 and CAP2 in bipolar disorder in a multiplex family. Bipolar Disord. 22, 70–78.

Aspit, L., Levitas, A., Etzion, S., Krymko, H., Slanovic, L., Zarivach, R., Etzion, Y., Parvari, R., 2019. CAP2 mutation leads to impaired actin dynamics and associates with supraventricular tachycardia and dilated cardiomyopathy. J. Med. Genet. 56, 228–235.

Balcer, H.I., Goodman, A.L., Rodal, A.A., Smith, E., Kugler, J., Heuser, J.E., Goode, B.L., 2003. Coordinated regulation of actin filament turnover by a high-molecular-weight Srv2/CAP complex, cofilin, profilin, and Aip1. Curr. Biol. 13, 2159–2169.

Bamburg, J.R., Minamide, L.S., Wiggan, O., Tahtamouni, L.H., Kuhn, T.B., 2021. Cofilin and actin dynamics: multiple modes of regulation and their impacts in neuronal development and degeneration. Cells 10, 2726.

Banker, B.Q., Engel, A.G., 1986. Basic reactions of muscle. In: Banker, B.Q., Engel, A.G. (Eds.), Myology: Basic and Clinical. McGraw-Hill, New York, pp. 845–907.

Benlali, A., Draskovic, I., Hazelett, D.J., Treisman, J.E., 2000. act up controls actin polymerization to alter cell shape and restrict Hedgehog signaling in the Drosophila eye disc. Cell 101, 271–281.

Bertling, E., Hotulainen, P., Mattila, P.K., Matilainen, T., Salminen, M., Lappalainen, P., 2004. Cyclase-associated protein 1 (CAP1) promotes cofilin-induced actin dynamics in mammalian nonmuscle cells. Mol. Biol. Cell 15, 2324–2334.

Bertling, E., Quintero-Monzon, O., Mattila, P.K., Goode, B.L., Lappalainen, P., 2007. Mechanism and biological role of profilin-Srv2/CAP interaction. J. Cell Sci. 120, 1225–1234.

Besser, R., Treese, N., Bohl, J., Goebel, H.H., 1994. Clinical, neurophysiologic and biopsy findings in neurotoxic amiodarone syndrome. Med Klin. 89, 367–372.

Bethlem, J., Vanwijngaarden, G.K., 1963. The incidence of ringed fibres and sarcoplasmic masses in normal and diseased muscle. J. Neurol. Neurosurg. Psychiatry 26, 326–332.

Bockhorn, J., Yee, K., Chang, Y.F., Prat, A., Huo, D., Nwachukwu, C., Dalton, R., Huang, S., Swanson, K.E., Perou, C.M., Olopade, O.I., Clarke, M.F., Greene, G.L., Liu, H., 2013. MicroRNA-30c targets cytoskeleton genes involved in breast cancer cell invasion. Breast Cancer Res Treat. 137, 373–382.

Bokarewa, M., Nagaev, I., Dahlberg, L., Smith, U., Tarkowski, A., 2005. Resistin, an adipokine with potent proinflammatory properties. J. Immunol. 174, 5789–5795.

Bosch, M., Castro, J., Saneyoshi, T., Matsuno, H., Sur, M., Hayashi, Y., 2014. Structural and molecular remodeling of dendritic spine substructures during long-term potentiation. Neuron 82, 444–459.

Boyer, O., Nevo, F., Plaisier, E., Funalot, B., Gribouval, O., Benoit, G., Huynh Cong, E., Arrondel, C., Tete, M.J., Montjean, R., Richard, L., Karras, A., Pouteil-Noble, C., Balafrej, L., Bonnardeaux, A., Canaud, G., Charasse, C., Dantal, J., Deschenes, G., Deteix, P., Dubourg, O., Petiot, P., Pouthier, D., Leguern, E., Guiochon-Mantel, A., Broutin, I., Gubler, M.C., Saunier, S., Ronco, P., Vallat, J.M., Alonso, M.A., Antignac, C., Mollet, G., 2011. INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. N. Engl. J. Med. 365, 2377–2388.

Bremer, A., Schoumans, J., Nordenskjold, M., Anderlid, B.M., Giacobini, M., 2009. An interstitial deletion of 7.1Mb in chromosome band 6p22.3 associated with developmental delay and dysmorphic features including heart defects, short neck, and eye abnormalities. Eur. J. Med Genet. 52, 358–362.

Brown, E.J., Schlondorff, J.S., Becker, D.J., Tsukaguchi, H., Tonna, S.J., Uscinski, A.L., Higgs, H.N., Henderson, J.M., Pollak, M.R., 2010. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. Nat. Genet. 42, 72–76.

Burnett, M.S., Lee, C.W., Kinnaird, T.D., Stabile, E., Durrani, S., Dullum, M.K., Devaney, J.M., Fishman, C., Stamou, S., Canos, D., Zbinden, S., Clavijo, L.C., Jang, G. J., Andrews, J.A., Zhu, J., Epstein, S.E., 2005. The potential role of resistin in atherogenesis. Atherosclerosis 182, 241–248.

Carpenter, S., Karpati, G., 1984. Patholohy of Skeletal Muscle. Churchill Livingston, New York,, New York, pp. 216–220.

Celestino-Soper, P.B., Skinner, C., Schroer, R., Eng, P., Shenai, J., Nowaczyk, M.M., Terespolsky, D., Cushing, D., Patel, G.S., Immken, L., Willis, A., Wiszniewska, J., Matalon, R., Rosenfeld, J.A., Stevenson, R.E., Kang, S.H., Cheung, S.W., Beaudet, A. L., Stankiewicz, P., 2012. Deletions in chromosome 6p22.3-p24.3, including ATXN1, are associated with developmental delay and autism spectrum disorders. Mol. Cytogenet. 5, 17.

Chaudhry, F., Little, K., Talarico, L., Quintero-Monzon, O., Goode, B.L., 2010. A central role for the WH2 domain of Srv2/CAP in recharging actin monomers to drive actin turnover in vitro and in vivo. Cytoskeleton 67, 120–133.

Chaudhry, F., Breitsprecher, D., Little, K., Sharov, G., Sokolova, O., Goode, B.L., 2013. Srv2/cyclase-associated protein forms hexameric shurikens that directly catalyze actin filament severing by cofilin. Mol. Biol. Cell 24, 31–41.

Chaudhry, F., Jansen, S., Little, K., Suarez, C., Boujemaa-Paterski, R., Blanchoin, L., Goode, B.L., 2014. Autonomous and in Trans functions for the two halves of Srv2/CAP in promoting actin turnover. Cytoskeleton 71, 351–360.

Cheema, H., Bertoli-Avella, A.M., Skrahina, V., Anjum, M.N., Waheed, N., Saeed, A., Beetz, C., Perez-Lopez, J., Rocha, M.E., Alawbathani, S., Pereira, C., Hovakimyan, M., Patric, I.R.P., Paknia, O., Ameziane, N., Cozma, C., Bauer, P., Rolfs, A., 2020. Genomic testing in 1019 individuals from 349 Pakistani families results in high diagnostic yield and clinical utility. NPJ Genom. Med. 5, 44.

Cingolani, L.A., Goda, Y., 2008. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat. Rev. Neurosci. 9, 344–356.

Colpan, M., Iwanski, J., Gregorio, C.C., 2021. CAP2 is a regulator of actin pointed end dynamics and myofibrillogenesis in cardiac muscle. Commun. Biol. 4, 365.

Conen, P.E., Murphy, E.G., Donohue, W.L., 1963. Light and electron microscopic studies of "myogranules" in a child with hypotonia and muscle weakness. Can. Med. Assoc. J. 89, 983–986.
Consitt, L.A., Bell, J.A., Houmard, J.A., 2009. Intramuscular lipid metabolism, insulin action, and obesity. IUBMB Life 61, 47–55.
Davies, A.F., Mirza, G., Sekhon, G., Turnpenny, P., Leroy, F., Speleman, F., Law, C., van Regemorter, N., Vamos, E., Flinter, F., Ragoussis, J., 1999. Delineation of two distinct 6p deletion syndromes. Hum. Genet. 104, 64–72.
Del Bigio, M.R., Jay, V., 1992. Inclusion body myositis with abundant ring fibers. Acta Neuropathol. 85, 105–110.
Di Maio, A., De Rosa, A., Pelucchi, S., Garofalo, M., Marciano, B., Nuzzo, T., Gardoni, F., Isidori, A.M., Di Luca, M., Errico, F., De Bartolomeis, A., Marcello, E., Usiello, A., 2022. Analysis of mRNA and protein levels of CAP2, DLG1 and ADAM10 genes in post-mortem brain of schizophrenia, Parkinson's and alzheimer's disease patients. Int J. Mol. Sci. 23, 1539.
Dirkx, E., da Costa Martins, P.A., De Windt, L.J., 2013. Regulation of fetal gene expression in heart failure. Biochim. Biophys. Acta 1832, 2414–2424.
Drozdz, D., Alvarez-Pitti, J., Wojcik, M., Borghi, C., Gabbianelli, R., Mazur, A., Herceg-Cavrak, V., Lopez-Valcarcel, B.G., Brzezinski, M., Lurbe, E., Wuhl, E., 2021. Obesity and cardiometabolic risk factors: from childhood to adulthood. Nutrients 13, 4176.
Fattori, F., Fiorillo, C., Rodolico, C., Tasca, G., Verardo, M., Bellacchio, E., Pizzi, S., Ciolfi, A., Fagiolari, G., Lupica, A., Broda, P., Pedemonte, M., Moggio, M., Bruno, C., Tartaglia, M., Bertini, E., D'Amico, A., 2018. Expanding the histopathological spectrum of CFL2-related myopathies. Clin. Genet. 93, 1234–1239.
Fedor-Chaiken, M., Deschenes, R.J., Broach, J.R., 1990. SRV2, a gene required for RAS activation of adenylate cyclase in yeast. Cell 61, 329–340.
Ferron, F., Rebowski, G., Lee, S.H., Dominguez, R., 2007. Structural basis for the recruitment of profilin-actin complexes during filament elongation by Ena/VASP. EMBO J. 26, 4597–4606.
Field, J., Nikawa, J., Broek, D., MacDonald, B., Rodgers, L., Wilson, I.A., Lerner, R.A., Wigler, M., 1988. Purification of a RAS-responsive adenylyl cyclase complex from Saccharomyces cerevisiae by use of an epitope addition method. Mol. Cell. Biol. 8, 2159–2165.
Field, J., Vojtek, A., Ballester, R., Bolger, G., Colicelli, J., Ferguson, K., Gerst, J., Kataoka, T., Michaeli, T., Powers, S., et al., 1990. Cloning and characterization of CAP, the S. cerevisiae gene encoding the 70 kd adenylyl cyclase-associated protein. Cell 61, 319–327.
Field, J., Ye, D.Z., Shinde, M., Liu, F., Schillinger, K.J., Lu, M., Wang, T., Skettini, M., Xiong, Y., Brice, A.K., Chung, D.C., Patel, V.V., 2015. CAP2 in cardiac conduction, sudden cardiac death and eye development. Sci. Rep. 5, 17256.
Finsterer, J., Stollberger, C., 2015. Review of cardiac disease in nemaline myopathy. Pedia Neurol. 53, 473–477.
Fowler, V.M., Dominguez, R., 2017. Tropomodulins and leiomodins: actin pointed end caps and nucleators in muscles. Biophys. J. 112, 1742–1760.
Freeman, N.L., Lila, T., Mintzer, K.A., Chen, Z., Pahk, A.J., Ren, R., Drubin, D.G., Field, J., 1996. A conserved proline-rich region of the Saccharomyces cerevisiae cyclase-associated protein binds SH3 domains and modulates cytoskeletal localization. Mol. Cell Biol. 16, 548–556.
Funk, J., Merino, F., Venkova, L., Heydenreich, L., Kierfeld, J., Vargas, P., Raunser, S., Piel, M., Bieling, P., 2019. Profilin and formin constitute a pacemaker system for robust actin filament growth. eLife 8, e50963.
Goode, B.L., Drubin, D.G., Lappalainen, P., 1998. Regulation of the cortical actin cytoskeleton in budding yeast by twinfilin, a ubiquitous actin monomer-sequestering protein. J. Cell Biol. 142, 723–733.
Goodson, M., Rust, M.B., Witke, W., Bannerman, D., Mott, R., Ponting, C.P., Flint, J., 2012. Cofilin-1: a modulator of anxiety in mice. PLOS Genet. 8, e1002970.
Gurniak, C.B., Chevessier, F., Jokwitz, M., Jonsson, F., Perlas, E., Richter, H., Matern, G., Boyl, P.P., Chaponnier, C., Furst, D., Schroder, R., Witke, W., 2014. Severe protein aggregate myopathy in a knockout mouse model points to an essential role of cofilin2 in sarcomeric actin exchange and muscle maintenance. Eur. J. Cell Biol. 93, 252–266.
Gurunathan, S., Sebastian, J., Baker, J., Abdel-Hamid, H.Z., West, S.C., Feingold, B., Peche, V., Reyes-Mugica, M., Madan-Khetarpal, S., Field, J., 2021. A homozygous CAP2 pathogenic variant in a neonate presenting with rapidly progressive cardiomyopathy and nemaline rods. Am. J. Med. Genet. A, 2021 Dec 04, Epub ahead of print.
Hakala, M., Wioland, H., Tolonen, M., Kotila, T., Jegou, A., Romet-Lemonne, G., Lappalainen, P., 2021. Twinfilin uncaps filament barbed ends to promote turnover of lamellipodial actin networks. Nat. Cell Biol. 23, 147–159.
Hansson, G.K., 2005. Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 352, 1685–1695.
Hershberger, R.E., Hedges, D.J., Morales, A., 2013. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat. Rev. Cardiol. 10, 531–547.
Hilton, D., Aguilar, R., Johnston, A., Goode, B., 2018. Species-specific functions of twinfilin in actin filament depolymerization. J. Mol. Biol. 430, 3323–3336.
Hotulainen, P., Hoogenraad, C.C., 2010. Actin in dendritic spines: connecting dynamics to function. J. Cell Biol. 189, 619–629.
Hubberstey, A.V., Mottillo, E.P., 2002. Cyclase-associated proteins: CAPacity for linking signal transduction and actin polymerization. FASEB J. 16, 487–499.
Iwanski, J., Gregorio, C.C., Colpan, M., 2021. Redefining actin dynamics of the pointed-end complex in striated muscle. Trends Cell Biol. 31, 708–711.
Jang, H.D., Lee, S.E., Yang, J., Lee, H.C., Shin, D., Lee, H., Lee, J., Jin, S., Kim, S., Lee, S. J., You, J., Park, H.W., Nam, K.Y., Lee, S.H., Park, S.W., Kim, J.S., Kim, S.Y., Kwon, Y.W., Kwak, S.H., Yang, H.M., Kim, H.S., 2019. Cyclase-associated protein 1 is a binding partner of proprotein convertase subtilisin/kexin type-9 and is required for the degradation of low-density lipoprotein receptors by proprotein convertase subtilisin/kexin type-9. Eur. Heart J. 41, 239–252.
Jansen, S., Collins, A., Golden, L., Sokolova, O., Goode, B.L., 2014. Structure and mechanism of mouse cyclase-associated protein (CAP1) in regulating actin dynamics. J. Biol. Chem. 289, 30732–30742.
Johnston, A.B., Collins, A., Goode, B.L., 2015. High-speed depolymerization at actin filament ends jointly catalysed by Twinfilin and Srv2/CAP. Nat. Cell Biol. 17, 1504–1511.
Joyce, N.C., Oskarsson, B., Jin, L.W., 2012. Muscle biopsy evaluation in neuromuscular disorders. Phys. Med Rehabil. Clin. N. Am. 23, 609–631.
Jung, H.S., Park, K.H., Cho, Y.M., Chung, S.S., Cho, H.J., Cho, S.Y., Kim, S.J., Kim, S.Y., Lee, H.K., Park, K.S., 2006. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc. Res. 69, 76–85.
Kaneko, S., Iida, R.H., Suga, T., Fukui, T., Morito, M., Yamane, A., 2011. Changes in triacylglycerol-accumulated fiber type, fiber type composition, and biogenesis in the mitochondria of the soleus muscle in obese rats. Anat. Rec. 294, 1904–1912.
Kemp, J.G., Blazev, R., Stephenson, D.G., Stephenson, G.M., 2009. Morphological and biochemical alterations of skeletal muscles from the genetically obese (ob/ob) mouse. Int J. Obes. 33, 831–841.
Kepser, L.J., Damar, F., De Cicco, T., Chaponnier, C., Proszynski, T.J., Pagenstecher, A., Rust, M.B., 2019. CAP2 deficiency delays myofibril actin cytoskeleton differentiation and disturbs skeletal muscle architecture and function. Proc. Natl. Acad. Sci. USA 116, 8397–8402.
Kepser, L.J., Khudayberdiev, S., Hinojosa, L.S., Macchi, C., Ruscica, M., Marcello, E., Culmsee, C., Grosse, R., Rust, M.B., 2021. Cyclase-associated protein 2 (CAP2) controls MRTF-A localization and SRF activity in mouse embryonic fibroblasts. Sci. Rep. 11, 4789.
Kosmas, K., Eskandarnaz, A., Khorsandi, A.B., Kumar, A., Ranjan, R., Eming, S.A., Noegel, A.A., Peche, V.S., 2015. CAP2 is a regulator of the actin cytoskeleton and its absence changes infiltration of inflammatory cells and contraction of wounds. Eur. J. Cell Biol. 94, 32–45.
Kotila, T., Kogan, K., Enkavi, G., Guo, S., Vattulainen, I., Goode, B.L., Lappalainen, P., 2018. Structural basis of actin monomer re-charging by cyclase-associated protein. Nat. Commun. 9, 1892.
Kotila, T., Wioland, H., Enkavi, G., Kogan, K., Vattulainen, I., Jegou, A., Romet-Lemonne, G., Lappalainen, P., 2019. Mechanism of synergistic actin filament pointed end depolymerization by cyclase-associated protein and cofilin. Nat. Commun. 10, 5320.
Kremneva, E., Makkonen, M.H., Skwarek-Maruszewska, A., Gateva, G., Michelot, A., Dominguez, R., Lappalainen, P., 2014. Cofilin-2 controls actin filament length in muscle sarcomeres. Dev. Cell 31, 215–226.
Kumar, A., Paeger, L., Kosmas, K., Kloppenburg, P., Noegel, A.A., Peche, V.S., 2016. Neuronal actin dynamics, spine density and neuronal dendritic complexity are regulated by CAP2. Front Cell Neurosci. 10, 180.
Lee, S., Lee, H.C., Kwon, Y.W., Lee, S.E., Cho, Y., Kim, J., Lee, S., Kim, J.Y., Lee, J., Yang, H.M., Mook-Jung, I., Nam, K.Y., Chung, J., Lazar, M.A., Kim, H.S., 2014. Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes. Cell Metab. 19, 484–497.
Leite, S.C., Pinto-Costa, R., Sousa, M.M., 2021. Actin dynamics in the growth cone: a key player in axon regeneration. Curr. Opin. Neurobiol. 69, 11–18.
Lewis, D.A., Levitt, P., 2002. Schizophrenia as a disorder of neurodevelopment. Annu Rev. Neurosci. 25, 409–432.
Lila, T., Drubin, D.G., 1997. Evidence for physical and functional interactions among two Saccharomyces cerevisiae SH3 domain proteins, an adenylyl cyclase-associated protein and the actin cytoskeleton. Mol. Biol. Cell 8, 367–385.
Macchi, C., Ferri, N., Sirtori, C.R., Corsini, A., Banach, M., Ruscica, M., 2021. Proprotein convertase subtilisin/kexin type 9: a view beyond the canonical cholesterol-lowering impact. Am. J. Pathol. 191, 1385–1397.
Makkonen, M., Bertling, E., Chebotareva, N.A., Baum, J., Lappalainen, P., 2013. Mammalian and malaria parasite cyclase-associated proteins catalyze nucleotide exchange on G-actin through a conserved mechanism. J. Biol. Chem. 288, 984–994.
Martins-de-Souza, D., Maccarrone, G., Wobrock, T., Zerr, I., Gormanns, P., Reckow, S., Falkai, P., Schmitt, A., Turck, C.W., 2010. Proteome analysis of the thalamus and cerebrospinal fluid reveals glycolysis dysfunction and potential biomarkers candidates for schizophrenia. J. Psychiatr. Res. 44, 1176–1189.
Mattila, P.K., Quintero-Monzon, O., Kugler, J., Moseley, J.B., Almo, S.C., Lappalainen, P., Goode, B.L., 2004. A high-affinity interaction with ADP-actin monomers underlies the mechanism and in vivo function of Srv2/cyclase-associated protein. Mol. Biol. Cell 15, 5158–5171.
McGrath, J., Roy, P., Perrin, B.J., 2017. Stereocilia morphogenesis and maintenance through regulation of actin stability. Semin. Cell Dev. Biol. 65, 88–95.
Meacham, C., Ho, E.E., Dubrovsky, E., Gertler, F.B., Hemann, M.T., 2009. In vivo RNAi screening identifies regulators of actin dynamics as key determinants of lymphoma progression. Nat. Genet. 41, 1133–1137.
Moriyama, K., Yahara, I., 2002. Human CAP1 is a key factor in the recycling of cofilin and actin for rapid actin turnover. J. Cell Sci. 115, 1591–1601.
Murray, R.M., Bhavsar, V., Tripoli, G., Howes, O., 2017. 30 years on: how the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. Schizophr. Bull. 43, 1190–1196.
Musovic, S., Shrestha, M.M., Komai, A.M., Olofsson, C.S., 2021. Resistin is co-secreted with adiponectin in white mouse adipocytes. Biochem. Biophys. Res. Commun. 534, 707–713.
Namme, J.N., Bepari, A.K., Takebayashi, H., 2021. Cofilin signaling in the CNS physiology and neurodegeneration. Int. J. Mol. Sci. 22, 10727.
Nieminen, M.S., Harjola, V.P., Hochadel, M., Drexler, H., Komajda, M., Brutsaert, D., Dickstein, K., Ponikowski, P., Tavazzi, L., Follath, F., Lopez-Sendon, J.L., 2008.

Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. Eur. J. Heart Fail 10, 140–148.
Nishida, Y., Shima, F., Sen, H., Tanaka, Y., Yanagihara, C., Yamawaki-Kataoka, Y., Kariya, K.I., Kataoka, T., 1998. Coiled-coil interaction of N-terminal 36 residues of cyclase-associated protein with adenylyl cyclase is sufficient for its function in Saccharomyces cerevisiae Ras pathway. J. Biol. Chem. 273, 28019–28024.
Nomura, K., Ono, K., Ono, S., 2012. CAS-1, a C. elegans cyclase-associated protein, is required for sarcomeric actin assembly in striated muscle. J. Cell Sci. 125, 4077–4089.
Ockeloen, C.W., Gilhuis, H.J., Pfundt, R., Kamsteeg, E.J., Agrawal, P.B., Beggs, A.H., Dara Hama-Amin, A., Diekstra, A., Knoers, N.V., Lammens, M., van Alfen, N., 2012. Congenital myopathy caused by a novel missense mutation in the CFL2 gene. Neuromuscul. Disord. 22, 632–639.
Ojala, P.J., Paavilainen, V.O., Vartiainen, M.K., Tuma, R., Weeds, A.G., Lappalainen, P., 2002. The two ADF-H domains of twinfilin play functionally distinct roles in interactions with actin monomers. Mol. Biol. Cell 13, 3811–3821.
Olson, E.N., Nordheim, A., 2010. Linking actin dynamics and gene transcription to drive cellular motile functions. Nat. Rev. Mol. Cell Biol. 11, 353–365.
Omotade, O.F., Pollitt, S.L., Zheng, J.Q., 2017. Actin-based growth cone motility and guidance. Mol. Cell Neurosci. 84, 4–10.
Ono, S., 2013. The role of cyclase-associated protein in regulating actin filament dynamics – more than a monomer-sequestration factor. J. Cell Sci. 126, 3249–3258.
Onuh, J.O., Qiu, H., 2020. The serum response factor/cofactors interactions and their implications in diseases. FEBS J. 288, 3120–3134.
Pappas, C.T., Mayfield, R.M., Henderson, C., Jamilpour, N., Cover, C., Hernandez, Z., Hutchinson, K.R., Chu, M., Nam, K.H., Valdez, J.M., Wong, P.K., Granzier, H.L., Gregorio, C.C., 2015. Knockout of Lmod2 results in shorter thin filaments followed by dilated cardiomyopathy and juvenile lethality. Proc. Natl. Acad. Sci. USA 112, 13573–13578.
Parlakian, A., Tuil, D., Hamard, G., Tavernier, G., Hentzen, D., Concordet, J.P., Paulin, D., Li, Z., Daegelen, D., 2004. Targeted inactivation of serum response factor in the developing heart results in myocardial defects and embryonic lethality. Mol. Cell Biol. 24, 5281–5289.
Parlakian, A., Charvet, C., Escoubet, B., Mericskay, M., Molkentin, J.D., Gary-Bobo, G., De Windt, L.J., Ludosky, M.A., Paulin, D., Daegelen, D., Tuil, D., Li, Z., 2005. Temporally controlled onset of dilated cardiomyopathy through disruption of the SRF gene in adult heart. Circulation 112, 2930–2939.
Patel, R., Peterson, R., 2019. Cardiomyopathy presenting prenatally with functional tricuspid and pulmonary atresia. Echocardiography 36, 1779–1782.
Paul, A.S., Pollard, T.D., 2008. The role of the FH1 domain and profilin in formin-mediated actin-filament elongation and nucleation. Curr. Biol. 18, 9–19.
Peche, V., Shekar, S., Leichter, M., Korte, H., Schroder, R., Schleicher, M., Holak, T.A., Clemen, C.S., Ramanath, Y.B., Pfitzer, G., Karakesisoglou, I., Noegel, A.A., 2007. CAP2, cyclase-associated protein 2, is a dual compartment protein. Cell Mol. Life Sci. 64, 2702–2715.
Peche, V.S., Holak, T.A., Burgute, B.D., Kosmas, K., Kale, S.P., Wunderlich, F.T., Elhamine, F., Stehle, R., Pfitzer, G., Nohroudi, K., Addicks, K., Stockigt, F., Schrickel, J.W., Gallinger, J., Schleicher, M., Noegel, A.A., 2012. Ablation of cyclase-associated protein 2 (CAP2) leads to cardiomyopathy. Cell Mol. Life Sci. 70, 527–543.
Pelucchi, S., Stringhi, R., Marcello, E., 2020a. Dendritic spines in Alzheimer's disease: how the actin cytoskeleton contributes to synaptic failure. Int J. Mol. Sci. 21, 908.
Pelucchi, S., Vandermeulen, L., Pizzamiglio, L., Aksan, B., Yan, J., Konietzny, A., Bonomi, E., Borroni, B., Padovani, A., Rust, M.B., Di Marino, D., Mikhaylova, M., Mauceri, D., Antonucci, F., Edefonti, V., Gardoni, F., Di Luca, M., Marcello, E., 2020b. Cyclase-associated protein 2 dimerization regulates cofilin in synaptic plasticity and Alzheimer's disease. Brain Commun. 2, fcaa086.
Peng, A.W., Belyantseva, I.A., Hsu, P.D., Friedman, T.B., Heller, S., 2009. Twinfilin 2 regulates actin filament lengths in cochlear stereocilia. J. Neurosci. 29, 15083–15088.
Quinn, S.N., Graves, S.H., Dains-McGahee, C., Friedman, E.M., Hassan, H., Witkowski, P., Sabbatini, M.E., 2017. Adenylyl cyclase 3/adenylyl cyclase-associated protein 1 (CAP1) complex mediates the anti-migratory effect of forskolin in pancreatic cancer cells. Mol. Carcinog. 56, 1344–1360.
Quintero-Monzon, O., Jonasson, E.M., Bertling, E., Talarico, L., Chaudhry, F., Sihvo, M., Lappalainen, P., Goode, B.L., 2009. Reconstitution and dissection of the 600-kDa Srv2/CAP complex: roles for oligomerization and cofilin-actin binding in driving actin turnover. J. Biol. Chem. 284, 10923–10934.
Ravenscroft, G., Jackaman, C., Bringans, S., Papadimitriou, J.M., Griffiths, L.M., McNamara, E., Bakker, A.J., Davies, K.E., Laing, N.G., Nowak, K.J., 2011. Mouse models of dominant ACTA1 disease recapitulate human disease and provide insight into therapies. Brain 134, 1101–1115.
Reilly, M.P., Lehrke, M., Wolfe, M.L., Rohatgi, A., Lazar, M.A., Rader, D.J., 2005. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 111, 932–939.
Ritov, V.B., Menshikova, E.V., Azuma, K., Wood, R., Toledo, F.G., Goodpaster, B.H., Ruderman, N.B., Kelley, D.E., 2010. Deficiency of electron transport chain in human skeletal muscle mitochondria in type 2 diabetes mellitus and obesity. Am. J. Physiol. Endocrinol. Metab. 298, E49–E58.
Rosen, S.M., Joshi, M., Hitt, T., Beggs, A.H., Agrawal, P.B., 2020. Knockin mouse model of the human CFL2 p.A35T mutation results in a unique splicing defect and severe myopathy phenotype. Hum. Mol. Genet. 29, 1996–2003.
Rust, M.B., 2015. ADF/cofilin: a crucial regulator of synapse physiology and behavior. Cell Mol. Life Sci. 72, 3521–3529.
Rust, M.B., Maritzen, T., 2015. Relevance of presynaptic actin dynamics for synapse function and mouse behavior. Exp. Cell Res. 335, 165–171.
Rust, M.B., Gurniak, C.B., Renner, M., Vara, H., Morando, L., Gorlich, A., Sassoe-Pognetto, M., Banchaabouchi, M.A., Giustetto, M., Triller, A., Choquet, D., Witke, W., 2010. Learning, AMPA receptor mobility and synaptic plasticity depend on n-cofilin-mediated actin dynamics. EMBO J. 29, 1889–1902.
Rust, M.B., Kullmann, J.A., Witke, W., 2012. Role of the actin-binding protein profilin1 in radial migration and glial cell adhesion of granule neurons in the cerebellum. Cell Adhes. Migr. 6, 1–5.
Rust, M.B., Khudayberdiev, S., Pelucchi, S., Marcello, E., 2020. CAPt`n of actin dynamics: recent advances in the molecular, developmental and physiological functions of cyclase-associated protein (CAP). Front. Cell Dev. Biol. 8, 586631.
von Schantz, C., Saharinen, J., Kopra, O., Cooper, J.D., Gentile, M., Hovatta, I., Peltonen, L., Jalanko, A., 2008. Brain gene expression profiles of Cln1 and Cln5 deficient mice unravels common molecular pathways underlying neuronal degeneration in NCL diseases. BMC Genom. 9, 146.
Schneider, F., Duong, T.A., Metz, I., Winkelmeier, J., Hubner, C.A., Endesfelder, U., Rust, M.B., 2021a. Mutual functional dependence of cyclase-associated protein 1 (CAP1) and cofilin1 in neuronal actin dynamics and growth cone function. Prog. Neurobiol. 202, 102050.
Schneider, F., Duong, T.A., Rust, M.B., 2021b. Neuron replating, a powerful and versatile approach to study early aspects of neuron differentiation. ENEURO 0536–20, 2021.
Schneider, F., Metz, I., Khudayberdiev, S., Rust, M.B., 2021c. Functional redundancy of cyclase-associated proteins CAP1 and CAP2 in differentiating neurons. Cells 10, 1525.
Shekhar, S., Chung, J., Kondev, J., Gelles, J., Goode, B.L., 2019. Synergy between cyclase-associated protein and cofilin accelerates actin filament depolymerization by two orders of magnitude. Nat. Commun. 10, 5319.
Shekhar, S., Hoeprich, G.J., Gelles, J., Goode, B.L., 2021. Twinfilin bypasses assembly conditions and actin filament aging to drive barbed end depolymerization. J. Cell Biol. 220, e202006022.
Shima, F., Yamawaki-Kataoka, Y., Yanagihara, C., Tamada, M., Okada, T., Kariya, K., Kataoka, T., 1997. Effect of association with adenylyl cyclase-associated protein on the interaction of yeast adenylyl cyclase with Ras protein. Mol. Cell Biol. 17, 1057–1064.
Shy, G.M., Engel, W.K., Somers, J.E., Wanko, T., 1963. Nemaline myopathy. A new congenital myopathy. Brain 86, 793–810.
Silswal, N., Singh, A.K., Aruna, B., Mukhopadhyay, S., Ghosh, S., Ehtesham, N.Z., 2005. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys. Res. Commun. 334, 1092–1101.
Skruber, K., Warp, P.V., Shklyarov, R., Thomas, J.D., Swanson, M.S., Henty-Ridilla, J.L., Read, T.A., Vitriol, E.A., 2020. Arp2/3 and Mena/VASP require profilin 1 for actin network assembly at the leading edge. Curr. Biol. 30, 2651–2664.
Stockigt, F., Peche, V.S., Linhart, M., Nickenig, G., Noegel, A.A., Schrickel, J.W., 2016. Deficiency of cyclase-associated protein 2 promotes arrhythmias associated with connexin43 maldistribution and fibrosis. Arch. Med. Sci. 12, 188–198.
Sun, Y.N., Huang, J.Q., Chen, Z.Z., Du, M., Ren, F.Z., Luo, J., Fang, B., 2020. Amyotrophy induced by a high-fat diet is closely related to inflammation and protein degradation determined by quantitative phosphoproteomic analysis in skeletal muscle of C57BL/6 J mice. J. Nutr. 150, 294–302.
Sungur, A.O., Stemmler, L., Wohr, M., Rust, M.B., 2018. Impaired object recognition but normal social behavior and ultrasonic communication in cofilin1 mutant mice. Front. Behav. Neurosci. 12, 25.
Taliun, D., Harris, D.N., Kessler, M.D., Carlson, J., Szpiech, Z.A., Torres, R., Taliun, S.A. G., Corvelo, A., Gogarten, S.M., Kang, H.M., Pitsillides, A.N., LeFaive, J., Lee, S.B., Tian, X., Browning, B.L., Das, S., Emde, A.K., Clarke, W.E., Loesch, D.P., Shetty, A.C., Blackwell, T.W., Smith, A.V., Wong, Q., Liu, X., Conomos, M.P., Bobo, D.M., Aguet, F., Albert, C., Alonso, A., Ardlie, K.G., Arking, D.E., Aslibekyan, S., Auer, P.L., Barnard, J., Barr, R.G., Barwick, L., Becker, L.C., Beer, R.L., Benjamin, E.J., Bielak, L. F., Blangero, J., Boehnke, M., Bowden, D.W., Brody, J.A., Burchard, E.G., Cade, B.E., Casella, J.F., Chalazan, B., Chasman, D.I., Chen, Y.I., Cho, M.H., Choi, S.H., Chung, M.K., Clish, C.B., Correa, A., Curran, J.E., Custer, B., Darbar, D., Daya, M., de Andrade, M., DeMeo, D.L., Dutcher, S.K., Ellinor, P.T., Emery, L.S., Eng, C., Fatkin, D., Fingerlin, T., Forer, L., Fornage, M., Franceschini, N., Fuchsberger, C., Fullerton, S.M., Germer, S., Gladwin, M.T., Gottlieb, D.J., Guo, X., Hall, M.E., He, J., Heard-Costa, N.L., Heckbert, S.R., Irvin, M.R., Johnsen, J.M., Johnson, A.D., Kaplan, R., Kardia, S.L.R., Kelly, T., Kelly, S., Kenny, E.E., Kiel, D.P., Klemmer, R., Konkle, B.A., Kooperberg, C., Kottgen, A., Lange, L.A., Lasky-Su, J., Levy, D., Lin, X., Lin, K.H., Liu, C., Loos, R.J.F., Garman, L., Gerszten, R., Lubitz, S.A., Lunetta, K.L., Mak, A.C.Y., Manichaikul, A., Manning, A.K., Mathias, R.A., McManus, D.D., McGarvey, S.T., Meigs, J.B., Meyers, D.A., Mikulla, J.L., Minear, M.A., Mitchell, B.D., Mohanty, S., Montasser, M.E., Montgomery, C., Morrison, A.C., Murabito, J.M., Natale, A., Natarajan, P., Nelson, S.C., North, K.E., O'Connell, J.R., Palmer, N.D., Pankratz, N., Peloso, G.M., Peyser, P.A., Pleiness, J., Post, W.S., Psaty, B.M., Rao, D. C., Redline, S., Reiner, A.P., Roden, D., Rotter, J.I., Ruczinski, I., Sarnowski, C., Schoenherr, S., Schwartz, D.A., Seo, J.S., Seshadri, S., Sheehan, V.A., Sheu, W.H., Shoemaker, M.B., Smith, N.L., Smith, J.A., Sotoodehnia, N., Stilp, A.M., Tang, W., Taylor, K.D., Telen, M., Thornton, T.A., Tracy, R.P., Van Den Berg, D.J., Vasan, R.S., Viaud-Martinez, K.A., Vrieze, S., Weeks, D.E., Weir, B.S., Weiss, S.T., Weng, L.C., Willer, C.J., Zhang, Y., Zhao, X., Arnett, D.K., Ashley-Koch, A.E., Barnes, K.C., Boerwinkle, E., Gabriel, S., Gibbs, R., Rice, K.M., Rich, S.S., Silverman, E.K., Qasba, P., Gan, W., Consortium, N.T.-Of.P.M., Papanicolaou, G.J., Nickerson, D.A., Browning, S.R., Zody, M.C., Zollner, S., Wilson, J.G., Cupples, L.A., Laurie, C.C., Jaquish, C.E., Hernandez, R.D., O'Connor, T.D., Abecasis, G.R., 2021. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed program. Nature 590, 290–299.

Thirion, C., Stucka, R., Mendel, B., Gruhler, A., Jaksch, M., Nowak, K.J., Binz, N., Laing, N.G., Lochmuller, H., 2001. Characterization of human muscle type cofilin (CFL2) in normal and regenerating muscle. Eur. J. Biochem. 268, 3473–3482.

Tondeleir, D., Vandamme, D., Vandekerckhove, J., Ampe, C., Lambrechts, A., 2009. Actin isoform expression patterns during mammalian development and in pathology: insights from mouse models. Cell Motil. Cytoskelet. 66, 798–815.

Vartiainen, M., Ojala, P., Auvinen, P., Peränen, J., Lappalainen, P., 2000. Mouse A6/twinfilin is an actin monomer-binding protein that localizes to the regions of rapid actin dynamics. Mol. Cell. Biol. 20, 1772–1783.

Vojtek, A., Haarer, B., Field, J., Gerst, J., Pollard, T.D., Brown, S., Wigler, M., 1991. Evidence for a functional link between profilin and CAP in the yeast S. cerevisiae. Cell 66, 497–505.

Wadmore, K., Azad, A.J., Gehmlich, K., 2021. The role of Z-disc proteins in myopathy and cardiomyopathy. Int. J. Mol. Sci. 22, 3058.

Wills, Z., Emerson, M., Rusch, J., Bikoff, J., Baum, B., Perrimon, N., Van Vactor, D., 2002. A drosophila homolog of cyclase-associated proteins collaborates with the Abl tyrosine kinase to control midline axon pathfinding. Neuron 36, 611–622.

de Winter, J.M., Ottenheijm, C.A.C., 2017. Sarcomere dysfunction in nemaline myopathy. J. Neuromuscul. Dis. 4, 99–113.

Wolf, M., Zimmermann, A.M., Gorlich, A., Gurniak, C.B., Sassoe-Pognetto, M., Friauf, E., Witke, W., Rust, M.B., 2015. ADF/cofilin controls synaptic actin dynamics and regulates synaptic vesicle mobilization and exocytosis. Cereb. Cortex 25, 2863–2875.

Wong, A.H., Lipska, B.K., Likhodi, O., Boffa, E., Weinberger, D.R., Kennedy, J.L., Van Tol, H.H., 2005. Cortical gene expression in the neonatal ventral-hippocampal lesion rat model. Schizophr. Res. 77, 261–270.

Xiong, Y., Bedi, K., Berritt, S., Attipoe, B.K., Brooks, T.G., Wang, K., Margulies, K.B., Field, J., 2019. Targeting MRTF/SRF in CAP2-dependent dilated cardiomyopathy delays disease onset. JCI Insight 4, e124629.

Yamazaki, K., Takamura, M., Masugi, Y., Mori, T., Du, W., Hibi, T., Hiraoka, N., Ohta, T., Ohki, M., Hirohashi, S., Sakamoto, M., 2009. Adenylate cyclase-associated protein 1 overexpressed in pancreatic cancers is involved in cancer cell motility. Lab Investig. 89, 425–432.

Yotti, R., Seidman, C.E., Seidman, J.G., 2019. Advances in the genetic basis and pathogenesis of sarcomere cardiomyopathies. Annu Rev. Genom. Hum. Genet 20, 129–153.

Zelicof, A., Gatica, J., Gerst, J.E., 1993. Molecular cloning and characterization of a rat homolog of CAP, the adenylyl cyclase-associated protein from Saccharomyces cerevisiae. J. Biol. Chem. 268, 13448–13453.

Zhang, X., Azhar, G., Chai, J., Sheridan, P., Nagano, K., Brown, T., Yang, J., Khrapko, K., Borras, A.M., Lawitts, J., Misra, R.P., Wei, J.Y., 2001. Cardiomyopathy in transgenic mice with cardiac-specific overexpression of serum response factor. Am. J. Physiol. Heart Circ. Physiol. 280, H1782–H1792.

Zhang, X., Cao, S., Barila, G., Edreira, M.M., Hong, K., Wankhede, M., Naim, N., Buck, M., Altschuler, D.L., 2018. Cyclase-associated protein 1 (CAP1) is a prenyl-binding partner of Rap1 GTPase. J. Biol. Chem. 293, 7659–7673.

Zhang, X., Pizzoni, A., Hong, K., Naim, N., Qi, C., Korkhov, V., Altschuler, D.L., 2021. CAP1 binds and activates adenylyl cyclase in mammalian cells. Proc. Natl. Acad. Sci. USA 118, e2024576118.

Zhu, Y., Wan, N., Shan, X., Deng, G., Xu, Q., Ye, H., Sun, Y., 2021. Celastrol targets adenylyl cyclase-associated protein 1 to reduce macrophages-mediated inflammation and ameliorates high fat diet-induced metabolic syndrome in mice. Acta Pharm. Sin. B 11, 1200–1212.

Zimmermann, A.M., Jene, T., Wolf, M., Gorlich, A., Gurniak, C.B., Sassoe-Pognetto, M., Witke, W., Friauf, E., Rust, M.B., 2015. Attention-deficit/hyperactivity disorder-like phenotype in a mouse model with impaired actin dynamics. Biol. Psychiatry 78, 95–106.