Cysteine String Protein (CSPα) is a presynaptic vesicle protein with neuroprotective activity. In humans, mutations in the DNAJC5 gene encoding CSPαs that produce heterozygous CSPα point mutations or point deletions cause autosomal-dominant, adult onset neuronal ceroid lipofuscinosis (ANCL), a neurodegenerative disorder characterized by accumulation of lysosomal cellular debris (Benitez et al., 2011; Nosková et al., 2011; Velinov et al., 2012). Disease onset is between 20–30 years of age and the course and outcome of ANCL involves, increased anxiety, speech difficulties, ataxia, involuntary movements, seizures, cognitive deterioration, dementia with a shortened life expectancy. In mice, CSPα KO causes activity-dependent synapse loss, progressive defects in neurotransmission and neurodegeneration verifying CSPα’s anti-neurodegenerative function (Fernández-Chacón et al., 2004; García-Junco-Clemente et al., 2010). CSPα heterozygote mice, which have reduced levels of CSPα, are phenotypically normal suggesting that wild type mice normally have “extra” CSPα protection (Fernández-Chacón et al., 2004). In Drosophila melanogaster, CSPα KO’s that survive to adulthood demonstrate temperature-sensitive paralysis, uncoordinated movement, shaking and early death (Zinsmaier et al., 1994). It is clear that the function of CSPα is to protect the synapse, what is not known is the mechanism(s) underlying the prevention of synapse loss by CSPα. Understandably, much effort has focused on delineating the cellular pathway of CSPα-mediated protection.

The CSPα Trimeric Complex

CSPα contains a “J-domain” which is a ~70-amino acid region of homology shared by bacterial DnaJ and all other J proteins as well as a palmitoylated cysteine-rich “string” region used for membrane attachment to the outer leaflet of synaptic vesicles (Braun and Scheller, 1995). Rather than being “constitutively active” CSPα becomes active upon assembly with SGT (small glutamine-rich tetratricopeptide repeat-containing protein) and Hsc70 (70-kDa heat-shock cognate protein) (Braun et al., 1996; Toeben et al., 2001). Hsc70 is a central hub of the cellular chaperone network (Craig et al., 2006; Kakkar et al., 2012), and it follows that collapse of Hsc70 would be expected to cause collapse of the J protein network. Each member of the J protein family—there are 49 J proteins in Homo sapiens—has a J domain that activates Hsc70’s ATPase activity for conformational work on diverse “client proteins” (Kakkar et al., 2012). Outside of the J domain, J proteins have little, if any, structural similarity. These non-homologous regions are, almost certainly, determinants of J protein specificity but do not provide much clarity into the functionality of specific J proteins. Since other J proteins do not compensate, CSPαs is generally viewed as facilitating highly specific folding events. In vitro, mutation of the invariant tripeptide of histidine, proline and aspartic acid (HPD motif) located between helices II and III of CSPα’s four α helical J domain creates a loss-of-function mutant that does not activate Hsc70 (Chamberlain and Burgoyne, 1997). CSPα is also found in non-neuronal secretory cells including exocrine (Braun and Scheller, 1995; Zhao et al., 1997; Weng et al., 2009), endocrine (Brown et al., 1998; Zhang et al., 2002) and neuroendocrine (Kohan et al., 1995; Chamberlain et al., 1996) secretory granules and mammary cell small vesicles (Gleave et al., 2001). That said, the reduced life-span in CSPα KO mice is due to neurodegeneration.
THE INTERVAL PRECEDING FULMINANT NEURODEGENERATION

CSPα KO mice appear normal at birth, but around postnatal day 20, they develop progressive motor deficits and CNS degeneration, followed by early lethality between days 40–80 (Fernández-Chacón et al., 2004). In this context it is noteworthy that CSPα is not required for neurotransmitter release but only necessary to maintain synaptic function and architecture. Which client proteins are critical for triggering the cascade of events leading to degeneration? The field is now turning to better appreciate the age interval of CSPα KO mice when the demise of the synapse is likely to begin. While this early window remains to be fully dissected, we know that around 20 proteins have altered expression patterns by P28 and that these proteins represent potential primary “misfolding events” (Zhang et al., 2012). Activity-dependent degeneration in mice and temperature-sensitive paralysis in Drosophila are distinguishing features of CSPα null models. In mice, synapses that fire frequently, such as those associated with photoreceptors and GABAergic neurons, are lost first (Schmitz et al., 2005). Of note, mice deficient in α-synuclein (α-SNARE, SNAP25 (synaptosomal associated protein of 25 kDa) expression is decreased in CSPα KO mice (Chandra et al., 2005; Zhang et al., 2012). However, it is the effective assembly/disassembly of SNAP25 into the SNAP complex during repeated rounds of exocytosis/endocytosis that correlates with the maintenance of synaptic function rather than cellular levels of SNAP25 (Sharma et al., 2011b, 2012a). While neurodegeneration is rescued by overexpression of wild-type, but not inactive mutants of SNAP-25, the decline in SNAP25 expression per se is unlikely to be a primary cause of neurodegeneration, as SNAP25 heterozygous mice with ~50% reduction in SNAP25 levels are phenotypically normal (Washbourne et al., 2002; Sharma et al., 2011b). Furthermore, the dramatic rescue of neurodegeneration in CSPα KO mice by α-synuclein, rescues the association of SNAP25 with other SNAREs but does not ameliorate the decrease in SNAP25 expression (Sharma et al., 2011b, 2012a). More recently, it was shown that treatment of CSPα KO mice with proteasome inhibitors reverses impairment of SNARE-complex assembly and alleviates neurodegeneration (Sharma et al., 2012b). CSPα has also been shown to interact with the t-SNARE, syntaxin (Nie et al., 1999; Evans et al., 2001) and the Ca2+ binding protein, synaptotagmin (Evans and Morgan, 2002), emphasizing its role in chaperoning the exocytosis machinery. Taken together, degeneration in CSPα KO mice is halted by interventions that correct SNARE complex function including interventions that influence SNARE complex assembly without elevating SNAP25 levels. A separate line of investigation has revealed that CSPα KO mice also have an endocytosis defect resulting in the failure to recycle and maintain the size of the synaptic vesicle pool during prolonged stimulation (Rozas et al., 2012). In fact, early on (P28) in the course of degeneration the GTPase, dynamin 1, which is essential for endocytosis, is reduced by ~40% in CSPα KO mice (Zhang et al., 2012). CSPα directly interacts with dynamin 1 to promote polymerization, a process required in membrane fission (Zhang et al., 2012), however the mechanistic details linking endocytosis and CSPα dysfunction remain to be established. Insights into exocytosis/endocytosis defects will undoubtedly prove to be important in understanding the pathological uncoupling between presynaptic exocytosis and endocytosis.

EXOCYTOSIS AND ENDOCYTOSIS MACHINERY

SNARE (soluble N-ethylmaleimide-sensitive factor attachment receptors) proteins are fundamental to presynaptic vesicle-release events and for that reason have been closely scrutinized as possible CSPα “clients”. The t-SNARE, SNAP25 (synaptosomal associated protein of 25 kDa) expression is decreased in CSPα KO mice (Chandra et al., 2005; Zhang et al., 2012). However, the “RESCUE” of CSPα KO MICE

Endogenous J proteins do not serve as “back ups” for the deletion of CSPα, however, overexpression of α-synuclein abrogates motor impairments and lethality in CSPα KO mice while KO of endogenous α-synuclein speeds up neurodegeneration (Chandra et al., 2005). Of note, mice deficient in α-synuclein do not have an obvious phenotype (Chandra et al., 2005). α-synuclein is a soluble presynaptic protein of unknown function that associates with synaptic vesicles and is the major component of Lewy bodies, a landmark of Parkinson’s disease and other neurodegenerative disorders (Maroteaux et al., 1988; Burre et al., 2010). CSPα/α-synuclein do not interact and Hsc70 ATPase is not activated by α-synuclein, hence, while CSPα and α-synuclein may target common “client proteins” they are nonetheless mechanistically distinct (Chandra et al., 2005). Somewhat paradoxically, treatment of CSPα KO mice with proteasome inhibitors ameliorates neurodegeneration and extends the life-span of CSPα KO mice (Sharma et al., 2012b). Thus, the neurodegeneration observed in CSPα KO mice is not due to a reduction in the proteasome capacity and the consequent elevation of ubiquitinated synaptic proteins. While the physiological implications of these findings have not yet been elucidated, rescue of degeneration in CSPα KO mice serves as proof-of-principle for intervention in nerve terminal failure and synapse loss and may pave the way for development of therapeutic agents that prevent neurodegeneration.

PRESYNAPTIC ION CHANNELS: CHANNEL PROTEOSTASIS AND MULTI-PROTEIN COMPLEXES

Do changes in presynaptic ion channels or ion channel complexes trigger the activity-dependent and temperature-dependent...
neurodegeneration in CSPα-KO mice? We have shown that large conductance Ca\(^{2+}\)-and voltage-activated K\(^+\) (BK) channels are \(\sim 2.5\) fold higher in the brain of CSPα null mice compared with age-matched wild types (Kyle et al., 2013). This increase in expression is observed at an early age (i.e., P23-P27), when levels of neuronal K\(_{1.1}\), K\(_{1.2}\) and Ca\(_{2.2}\) do not change. Physiologically, BK channels are activated by membrane depolarization and/or elevations in intracellular Ca\(^{2+}\) and drive the membrane potential towards the K\(^+\) equilibrium potential. Under normal conditions, BK channels regulate repolarization of the action potential, thereby regulating excitability of neurons, as well as presynaptic neurotransmitter release. Further, ectopic expression of dysfunctional CSPα mutants (i.e., CSP\(_{\text{HPD-AAA}}\), CSP\(_{\text{L116A}}\), CSP\(_{\text{L115R}}\)) also elicits elevation of BK channel expression and macroscopic current density (Kyle et al., 2013; Ahrendt et al., 2014) suggesting that the observed increase, at least initially, reflects an elevation of functional, rather than misfolded or aggregated BK channel protein. CSP\(_{\text{HPD-AAA}}\) is a loss-of-function mutant in which the essential J domain required for activation of Hsc70ATPase is disrupted but the cysteine string anchor is functional. The increase found in the presence of this loss-of-function mutant is consistent with the increase in BK channel expression observed in CSPα null mice. On the other hand, while CSP\(_{\text{L116A}}\) and CSP\(_{\text{L115R}}\) increase BK channel density at the membrane, the increase is not as large as that observed with CSP\(_{\text{HPD-AAA}}\) (Kyle et al., 2013), suggesting that CSP\(_{\text{L116A}}\) and CSP\(_{\text{L115R}}\) are partial loss-of-function mutants.

In humans, deletion of residue 116 or replacement of Lys115 by Arg in the cysteine string region results in ANCL (Benitez et al., 2011; Nosková et al., 2011; Velinov et al., 2012), however the mechanism(s) underlying disease pathology is not known. It is becoming increasingly clear that changes in the cysteine string region can promote oligomerization. Wild type CSPα self-associates (Braun and Scheller, 1995) and this dimerization is eliminated in the absence of the cysteine string region (Xu et al., 2010). When expressed in bacteria, which lack eukaryotic palmitoyltransferase enzymes, CSPα forms oligomers and the cysteine string region is important for the self-association (Swayne et al., 2003). Two mutations in the cysteine string region of CSPα, L116Δ and L115R, do not effectively anchor to synaptic vesicles and form oligomers indicating the cysteine string region is closely tied to oligomerization properties (Greaves et al., 2012). Clearly, identification of the neuronal location of CSP\(_{\text{L116A}}\)/CSP\(_{\text{L115R}}\) oligomers is central to understanding ANCL disease progression. Thus, disruption of the anchor to the synaptic vesicle while maintaining the functional J domain in the CSP\(_{\text{L116A}}\) and CSP\(_{\text{L115R}}\) mutants and subsequent CSPα oligomerization and cellular mislocalization likely leads to indiscriminate chaperone activity. We speculate that CSP\(_{\text{L116A}}\) and CSP\(_{\text{L115R}}\) cause both a partial loss-of-function (i.e., reduced chaperone activity at the synaptic vesicle) as well as gain-of-function (i.e., increased chaperone activity at a different cellular location). Consistent with this notion, CSPα heterozygote mice do not show neurodegeneration while ANCL patients show adult-onset neurodegeneration most likely due to mislocalized/oligomerized mutant CSPα chaperone activity outside the presynapse. Do changes in BK channel activity link to neurological disorders or neurodegeneration? Several studies have reported that alterations in the expression and function of BK channels give rise to neural dysfunction. For example, genetic deletion of BK channel subunits in mice (Sausbier et al., 2004; Brenner et al., 2005) and a gain-of-function channel mutation in humans (Du et al., 2005; Diez-Sampedro et al., 2006) are associated with ataxia and epilepsy, while functional alterations are associated with retardation, schizophrenia and autism (Laumonnier et al., 2006; Zhang et al., 2006; Higgins et al., 2008; Deng et al., 2013). Clearly, when BK channel activity is disrupted, neural excitability and neurotransmitter release are disrupted, but neurodegeneration per se does not typically ensue raising a number of interesting questions. Does the fulminant, activity-dependent neurodegeneration seen in CSPα KO mice result from a coupling of aberrant BK channel expression with synaptic vesicle release/recycling defects? What underlies the rapid rate of degeneration in CSPα KO mice. Further, are complexes of BK channels with other synaptic proteins regulated by CSPα? BK channels are subject to a wide array of regulatory processes, including interactions with SNARE proteins (Ling et al., 2003); however the precise details of these channel complexes in CSPα KO mice remain to be investigated. We speculate that CSPα directly modulates BK channel density, nonetheless this is not a foregone conclusion. Future experiments will undoubtedly establish whether CSPα acts indirectly via one of the known regulators of BK channel activity or by directly targeting the channels.

Do functional and/or structural changes in voltage-dependent Ca\(^{2+}\) channels occur early in the pathological sequence of events underlying neurodegeneration in CSPα KO mice? Whether CSPα directly regulates Ca\(^{2+}\) currents remains contentious. Ca\(^{2+}\) entry into presynaptic nerve terminals is fundamental to neurotransmission and consequently subject to multiple levels of control. A large body of work has clarified that neurotransmission defects at the neuromuscular junction involve a decrease in quantal content, a reduction in the calcium sensitivity of evoked exocytosis and anomalous bursts of spontaneous neurotransmitter release (Umbach et al., 1994; Zinsmaier et al., 1994; Dawson-Scully et al., 2000, 2007; Ruiz et al., 2008). Further, recruitment of Ca\(^{2+}\) channels (Chen et al., 2002) as well as physical interactions of CSPα with N-type and P/Q type voltage-dependent Ca\(^{2+}\) channels have been demonstrated (Leveque et al., 1998; Miller et al., 2003a,b; Swayne et al., 2005, 2006). Whether it is the synaptic vesicle-anchored monomeric CSPα or the mislocalized CSPα oligomers that regulate Ca\(^{2+}\) currents requires further investigation. We have found that CSPα influences the regulation of N-type Ca\(^{2+}\) channels by heterotrimeric GTP binding proteins (Maggia et al., 2000; Miller et al., 2003b; Natochin et al., 2005). There are still many unanswered questions regarding the role of CSPα in regulating synaptic channels and synaptic channel complexes. The CSPα KO mouse model offers an excellent opportunity to study channel proteostasis and channel complexes that may contribute to activity-dependent neurodegeneration. How CSPα might function in different secretory cells (e.g., pancreatic exocrine and endocrine cells), given the differences in their complement of ion channels, also remains to be determined. Further efforts will be needed to untangle the neuroprotective pathway(s) involving CSPα at the synapse and to establish precisely the complement
of synaptic channels involved in the cascade of neurodegenerative events triggered by the absence of CSPα.

In summary, ion channels are physiologically regulated within tight limits and present evidence implicates the presynaptic molecular chaperone CSPα in the fine-tuning of functional channel levels and regulation of synaptic channel complexes. In the future, it will be interesting to determine whether CSPα is also important for the quality control of misfolded/aberrant channels. The time course of the expression changes in SNAP25, dynamin 1 and synaptic channels in CSPα KO mice remains a key question.

**JEOPARDIZING THE SYNAPSE: LINKS TO ALZHEIMER’S AND PARKINSON’S DISEASE**

Clearly, the dysfunction of CSPα is linked to undesired consequences. Neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease show a characteristic loss of neurons and synapses (Muchowski and Wacker, 2005). The identification of CSPα as a central chaperone for the maintenance of synapses raises the questions: are cellular CSPα-neuroprotective pathways compromised in neurodegenerative disorders other than ANCL? Do functionally impaired proteins that build up in neurodegenerative disorders interfere with CSPα chaperone activity? It is noteworthy that lysosomal lipofuscin inclusions, like those seen in ANCL, are present in very early onset and unusually fast progressing dementia as well as lysosomal inclusions typically seen in Kufs disease.

**FUTURE PERSPECTIVES**

When CSPα is compromised, protein surveillance and proteostasis mechanisms in the neuron fail and the integrity of pre-synaptic terminals is compromised. The field is now poised to tackle in detail the pathogenic sequence of events responsible for activity-dependent neurodegeneration in the absence of CSPα chaperone activity. The emerging detailed molecular blueprint will undoubtedly serve investigators well in the development of therapeutics that protect against synaptic loss in neurodegenerative disorders.

**REFERENCES**

Ahrendt, E., Kyle, B., Braun, A. P., and Braun, J. E. (2014). Cysteine string protein limits expression of the large conductance, calcium-activated K(+) (BK) channel. PLoS One 9:e86586. doi: 10.1371/journal.pone.0086586

Arnold, C., Reich, N., Leibold, C., Becker, S., Prüfert, K., Sautter, K., et al. (2004). Structure-function analysis of the cysteine string protein in Drosophila: cysteine string, linker and C terminus. J. Exp. Biol. 207, 1323–1334. doi: 10.1242/jeb.00898

Benitez, B. A., Alvarado, D., Cai, Y., Mayo, K., Chakraverty, S., Norton, J., et al. (2011). Exome-sequencing confirms DNAJC5 mutations as cause of adult neuronal ceroid-lipofuscinosis. PLoS One 6:e26741. doi: 10.1371/journal.pone.0026741

Braun, J. E., and Scheller, R. H. (1995). Cysteine string protein, a DnaJ family member, is present on diverse secretory vesicles. Neuron 14, 1361–1369. doi: 10.1016/0896-6273(95)00114-1

Braun, J. E., Wilbanks, S. M., and Scheller, R. H. (1996). The cysteine string vesicle protein activates Hsc70 ATPase. J. Biol. Chem. 271, 25989–25993. doi: 10.1074/jbc.271.42.25989

Brenner, R., Chen, Q. H., Vilayuthong, A., Toney, G. M., Noebels, J. L., and Aldrich, R. W. (2005). BK channel beta4 subunit reduces dentate gyrus excitability and protects against temporal lobe seizures. Nat. Neurosci. 8, 1752–1759. doi: 10.1038/nn1573

Bronk, F., Nie, Z., Klose, M. D., Dawson-Scully, K., Zhang, J., Robertson, R. M., et al. (2005). The multiple functions of cysteine-string protein analyzed at Drosophila nerve terminals. J. Neurosci. 25, 2204–2214. doi: 10.1523/jneurosci.3610-04.2005

Brown, H., Larsson, O., Braestrup, R., Yang, S., Leibiger, B., Leibiger, I., et al. (1998). Cysteine string protein (CSPα) is an insulin secretory granule-associated protein regulating beta-cell exocytosis. EMBO J. 17, 5048–5058. doi: 10.1093/emboj/17.17.5048

Burre, I., Sharma, M., Tsitsenis, T., Buchman, V., Etherton, M. R., and Sudhof, T. C. (2010). Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. Science 329, 1663–1667. doi: 10.1126/science.1195227

Chamberlain, L. H., and Burgoyne, R. D. (1997). The molecular chaperone function of the secretory vesicle cysteine string proteins. J. Biol. Chem. 272, 31420–31426. doi: 10.1074/jbc.272.50.31420

Chamberlain, L. H., Henry, J., and Burgoyne, R. D. (1996). Cysteine string proteins are associated with chromaffin granules. J. Biol. Chem. 271, 19514–19517. doi: 10.1074/jbc.271.32.19514

Chandra, S., Gallardo, G., Fernandez-Chacon, R., Schluter, O. M., and Sudhof, T. C. (2005). Alpha-synuclein cooperates with CSP alpha in preventing neurodegeneration. Cell 123, 383–396. doi: 10.1016/j.cell.2005.09.028

Chen, S., Zheng, X., Schulze, K. L., Morris, T., Bellen, H., and Stanley, E. F. (2002). Enhancement of presynaptic calcium current by cysteine string protein. J. Physiol. 538, 383–389. doi: 10.1113/jphysiol.2001.01397

Craig, E. A., Huang, P., Aron, R., and Andrew, A. (2006). The diverse roles of J-proteins, the obligate Hsp70 co-chaperone. Rev. Physiol. Biochem. Pharmacol. 156, 1–21. doi: 10.1007/s00221-006-0001-0

Dawson-Scully, K., Bronk, P., Atwood, H. L., and Zinsmaier, K. E. (2005). Cysteine-string protein increases the calcium sensitivity of neurotransmitter exocytosis in Drosophila. J. Neurosci. 20, 6039–6047.

Dawson-Scully, K., Lin, Y., Imad, M., Zhang, J., Marin, L., Horne, J. A., et al. (2007). Morphological and functional effects of altered cysteine string protein at the Drosophila larval neuromuscular junction. Synapse 61, 1–16. doi: 10.1002/syn.20335

Deng, P. Y., Rotman, Z., Blundon, J. A., Cho, Y., Cui, J., Cavalli, V., et al. (2013). FMRP regulates neurotransmitter release and synaptic information transmission by modulating action potential duration via BK channels. Neuron 77, 696–711. doi: 10.1016/j.neuron.2012.12.018

Diez-Sampedro, A., Silverman, W. R., Bautista, J. F., and Richardson, G. B. (2006). Mechanism of increased open probability by a mutation of the BK channel. J. Neurophysiol. 96, 1507–1516. doi: 10.1152/jn.00461.2006

Dolzhanskaya, N., Gonzalez, M. A., Sperziani, E., Stefl, S., Messing, J., Wen, G. Y., et al. (2014). A novel p.Leu381Pro mutation in presenilin 1 is associated with very early onset and unusually fast progressing dementia as well as lysosomal inclusions typically seen in Kufs disease. J. Alzheimers Dis. 39, 23–27. doi: 10.3233/JAD-131340

Du, W., Bautista, J. F., Yang, H., Diiez-Sampedro, A., You, S. A., Wang, L., et al. (2005). Calcium-sensitive potassium channelopathy in human epilepsy and paroxysmal movement disorder. Nat. Genet. 37, 733–738. doi: 10.1038/ng1585

Evans, G. J., and Morgan, A. (2002). Phosphorylation-dependent interaction of the synaptic vesicle proteins cysteine string protein and synaptotagmin I. Biochem. J. 364, 343–347. doi: 10.1042/bj20020123

Evans, G. J., Wilkinson, M. C., Graham, M. E., Turner, K. M., Chamberlain, L. H., Burgoyne, R. D., et al. (2001). Phosphorylation of cysteine string protein by protein kinase A. Implications for the modulation of exocytosis. J. Biol. Chem. 276, 47877–47885. doi: 10.1074/jbc.M108186200

Fernández-Chacón, R., Wolfér, M., Nishimune, H., Tabares, L., Schnitz, F., Castellano-Munoz, M., et al. (2004). The synaptic vesicle protein CSP alpha prevents presynaptic degeneration. Neuron 42, 237–251. doi: 10.1016/j.neuron.2004.09.019-4
García-Junco-Clemente, P., Cantero, G., Gomez-Sanchez, L., Lineares-Clemente, P., Martinez-Lopez, J. A., Lujan, R., et al. (2010). Cysteine string protein-alpha prevents activity-dependent degeneration in GABAergic synapses. J. Neurosci. 30, 7377–7391. doi: 10.1523/jneurosci.0924-10.2010

Gleave, T. L., Beechey, R. B., and Burgoyne, R. D. (2001). Cysteine string protein expression in mammary epithelial cells. Pflugers Arch. 441, 639–649. doi: 10.1007/s004240000478

Greaves, J., Lemonidis, K., Gorleku, O. A., Cruchaga, C., Grefen, C., and Chamberlain, L. H. (2012). Palmitoylation-induced aggregation of cysteine-string protein mutants that cause neuronal ceroid lipofuscinosis. J. Biol. Chem. 287, 37330–37339. doi: 10.1074/jbc.m112.389098

Higgins, J. J., Hao, J., Kosofsky, B. E., and Rajadhyaksha, A. M. (2008). Disregulation of large-conductance Ca2+-activated K+ channel expression in nonsyn- dromal mental retardation due to a cebelin p.R419X mutation. Neurogenetics 9, 219–223. doi: 10.1007/s10048-008-0128-2

Kakkar, V., Prins, L. C., and Kampinga, H. H. (2012). DNAJ proteins and protein aggregation diseases. Curr. Top. Med. Chem. 12, 2473–2490. doi: 10.2174/15680261212220004

Kohan, S. A., Pescatori, M., Brecha, N. C., Mastrogiacomo, A., Umback, J. A., and Gundersen, C. B. (1995). Cysteine string protein immunoreactivity in the nervous system and adrenal gland of rat. J. Neurosci. 15, 6230–6238.

Kyle, B. D., Ahrendt, E., Braun, A. P., and Braun, J. E. (2013). The large con- ductance, calcium-activated K(+) channel is regulated by cysteine string protein. Sci. Rep. 3:2447. doi: 10.1038/srep02447

Laumonier, F., Roger, S., Guerin, P., Molinari, F., Mrad, R., Cahard, D., et al. (2006). Association of a functional deficit of the BKCa channel, a synaptic regulator of neuronal excitability, with autism and mental retardation. Am. J. Psychiatry 163, 1622–1629. doi: 10.1176/appi.ajp.163.9.1622

Leveque, C., Pupier, S., Marqueze, B., Geslin, L., Kataoka, M., Takahashi, M., et al. (1998). Interaction of cysteine string proteins with the alpha1A subunit of the P/Q-type calcium channel. J. Biol. Chem. 273, 13488–13492. doi: 10.1074/jbc.273.22.13488

Ling, S., Sheng, J.-Z., Braun, J. E. A., and Braun, A. P. (2003). Syntaxin 1A co-associates with native rat brain and cloned large conductance, calcium-activated K+ channels in situ. J. Physiol. 533, 65–81. doi: 10.1113/jphysiol.2003.051631

Maggi, J. M., Jarvis, S. E., Arnott, M. I., Zamponi, G. W., and Braun, J. E. (2000). Cysteine string protein regulates G-protein modulation of N-type calcium channels. Neuron 28, 195–204. doi: 10.1016/s0896-6273(00)00096-9

Maroteaux, L., Campanelli, J. T., and Scheller, R. H. (1988). Synuclein: a neuron- specific protein localized to the nucleus and presynaptic nerve terminal. J. Neurosci. 8, 2804–2815.

Miller, L. C., Swayne, L. A., Chen, L., Feng, Z. P., Wacker, J. L., Muchowski, P. J., et al. (2005). Cysteine string protein-alpha is essential for the high calcium sensitivity of exocytosis in a ver- tebrate synapse. Eur. J. Neurosci. 27, 3118–3131. doi: 10.1111/j.1460-9568.2008.05930.x

Saubier, M., Hu, H., Arnitz, C., Feil, S., Kamm, S., Adelsberger, H., et al. (2004). Cerebellar ataxia and Purkinje cell dysfunction caused by Ca2+-activated K+ channel deficiency. Proc. Natl. Acad. Sci. U S A 101, 9474–9478. doi: 10.1073/pnas.0401720101

Schmitz, F., Tabares, L., Khimich, D., Strenzke, N., de la Villa-Polo, P., Castellano-Munoz, M., et al. (2006). CSPAlpha-deficiency causes massive and rapid photoreceptor degeneration. Proc. Natl. Acad. Sci. U S A 103, 2926–2931. doi: 10.1073/pnas.0510060103

Sharma, M., Burre, J., and Sudhof, T. C. (2011b). CSPAlpha promotes SNARE complex assembly by chaperoning SNAP-25 during synaptic activity. Nat. Cell Biol. 13, 30–39. doi: 10.1038/ncco2111-182a

Sharma, M., Burre, J., Bronk, P., Zhang, Y., Xu, W., and Sudhof, T. C. (2012a). CSPAlpha knockout causes neurodegeneration by impairing SNAP-25 function. EMBO J. doi: 10.1038/embj.2011.467

Sharma, M., Burre, J., and Sudhof, T. C. (2012b). Proteasome inhibition alleviates SNARE-dependent neurodegeneration. Sci. Transl. Med. 4, 147ra113. doi: 10.1126/scitranslmed.3004028

Swayne, L. A., Beck, K. E., and Braun, J. E. (2006). The cysteine string protein multimeric complex. Biochem. Biophys. Res. Commun. 348, 85–91. doi: 10.1016/j.bbrc.2006.07.033

Swayne, L. A., Blatter, C., Kay, J. G., and Braun, J. E. A. (2003). Oligomerization characteristics of cysteine string protein. Biochem. Biophys. Res. Commun. 300, 921–926. doi: 10.1006/bbrc.2005.0701

Tobaben, S., Thakur, P., Fernandez-Chacon, R., Sudhof, T. C., Rettig, J., and Stahl, B. (2001). A trimeric protein complex functions as a synaptic chaperone machine. Neuron 31, 899–907. doi: 10.1016/s0896-6273(01)00427-5

Umbach, J. A., Zinsmaier, K. E., Eberle, K. K., Buchner, E., Benzer, S., and Chamberlain, L. H. (2012). Palmitoylation-induced aggregation of cysteine- string protein mutants that cause neuronal ceroid lipofuscinosis. Proc. Natl. Acad. Sci. U S A 109, 15057–15062. doi: 10.1073/pnas.1202009109
Zinsmaier, K. E., Eberle, K. K., Buchner, E., Walter, N., and Benzer, S. (1994). Paralysis and early death in cysteine string protein mutants of Drosophila. Science 263, 977–980. doi: 10.1126/science.8310297

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 March 2014; accepted: 09 April 2014; published online: 29 April 2014.

Citation: Donnelier J and Braun JEA (2014) CSPα—chaperoning presynaptic proteins. Front. Cell. Neurosci. 8:116. doi: 10.3389/fncel.2014.00116
This article was submitted to the journal Frontiers in Cellular Neuroscience. Copyright © 2014 Donnelier and Braun. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.