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The Role of Human Coactosin-Like Protein in Neurodegenerative Disorders

Y Anu Shanu[1,4,5], Antonio Lauto[2,3,5], Simon J Myers[1,3,4,5*]

Affiliation

[1]Neuro-Cell Biology Laboratory, Western Sydney University, Locked Bag 1797, Penrith, NSW 1797 Australia
[2]Biomedical Engineering & Neuroscience (BENS), Western Sydney University, Locked Bag 1797, Penrith South DC, NSW 1797 Australia
[3]School of Science and Health, Western Sydney University, Locked Bag 1797, Penrith, NSW 1797 Australia
[4]Medical Sciences Research Group, School of Medicine, Western Sydney University, Locked Bag 1797, Penrith, NSW 1797 Australia
[5]School of Medicine, Western Sydney University, Locked Bag 1797, Penrith, NSW 1797 Australia

***Corresponding author:** Simon J Myers, Neuro-Cell Biology Laboratory, Western Sydney University, Locked Bag 1797, Penrith, NSW 1797 Australia, Tel: +61-2-46203383, Fax: +61-2-46203025, Email: s.myers@uws.edu.au

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Abstract

Coactosin is one of the numerous actin-binding proteins which regulate the actin cytoskeleton. Coactosin binds F-actin, and also interacts with 5-lipoxygenase, which is the first committed enzyme in leukotriene biosynthesis. Coactosin and human coactosin like protein 1 (COTL1) have the potential to play a role in the degradation or impairment of neuronal cells and their functioning. Its homology to other proteins that affect neuronal cells also contributes to this notion. The objective of this review is to explore its structural novelty, regulation and its significance in neurodegenerative diseases.

Keywords: COTL1; Coactosin; 5'Lipoxygenase; Actin polymerisation; Hereditary Sensory Neuropathy; Neurodegeneration; Cytoskeleton

Introduction

Neurodegenerative disorders include some of the most common and least understood diseases characterised by impaired sensory, motor and/or mental functioning. Many, such as Alzheimer's disease, currently have no cure and subsequently have become the focus of significant research in searching for an understanding of the molecular pathophysiology of the disease and looking for methods of prevention, treatment and cure.

Neurodegenerative disorders are categorised by the loss of structure and/or function of neurons. Neuronal cell degeneration and death as well as plaques and atypical protein assemblies are the most common causes of such loss of structure and function (Heemels 2006). Neurons are made up of two morphologically defined regions: the dendrites and the axons. Microtubules, actin filaments and neurofilaments make up the neuronal cytoskeleton and are responsible for several critical roles including the formation of axons, intracellular transport of cargoes and maintenance of its structure (Kevenaar &Hoogenraad 2015).

Coactosin is a 17 kDa actin binding protein originally isolated from *Dictyostelium discoidum* but it has since been isolated from other organisms including humans, fruit flies and mice (Poukkula et al. 2011). Both coactosin and human coactosin like protein 1 (COTL1) can bind to 5-lipoxygenase (5-LO) and filamentous actin (F-actin) (Lackie 2007) and has the potential to play a role in the degradation or impairment of neuronal cells and their functioning. Its homology to other proteins that affect neuronal cells also contributes to this notion.

Structure of COTL1

Coactosin shows structural homology to actin-depolymerising factor (ADF-H) domain. The ADF homology domain, a highly conserved protein motif, promotes cytoskeletal dynamics by facilitating processes such as endocytosis, cell migration, morphogenesis and cytokinesis (Poukkula et al. 2011), owing to its binding affinity towards filamentous actin (F-actin) and not globular actin (G-actin). ADF domain consists of five internal β-sheets, of which β1- β4 are antiparallel and β4 is parallel to β5. The sheets are surrounded by four α-helices with α1-α3 parallel to the β-sheets and α4 packed perpendicular to the β3 and β4 sheets (Hellman et al. 2004).

Despite the similar structure, the amino acid sequence of COTL1 shows low homology to Coactosin with 33.3% sequence identity and

75% similarity (Liu et al. 2004). COTL1 is entirely composed of a single ADF domain and consists of five β-stranded sheets with two helices each on either side (Fig. 1A). The loop between β3-β4 is flexible while the other regions are held rigid (Rakonjac, 2009). Lys-75 and Lys-131, which corresponds to binding sites for F-actin and 5-LO respectively (Fig. 1B) lies close to each other suggesting overlapping binding sites, which has been suggested as a structural mechanism to prevent simultaneous binding (Liu et al 2004), which is also supported by the fact that a 5-LO-COTL1-F-Actin ternary complex has not yet been reported (Esser et al. 2010).

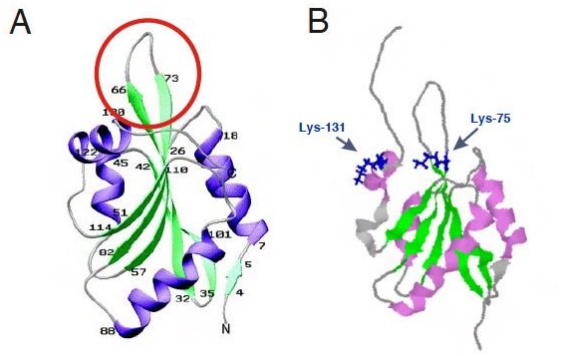

Figure 1: Structure of human COTL1.

1A shows the ribbon structure with β1- β5 sheets shown in green and α1-α4 helices in purple. The flexible β3- β4 loop is highlighted in red. 1B shows spatial alignment of Lys-75 and Lys-131, binding sites for F-actin and 5-LO respectively (Rakonjac, 2009).

COTL1 and Actin polymerisation

COTL1 plays several functional roles in normal physiology, however it is primarily identified as an actin binding protein due to its role in the promotion of actin polymerisation. Actin treadmilling is a dynamic process where ATP bound globular monomer actin (G-Actin) is added on to the '+' end of the growing filament by ADF-H protein Profilin, promoting actin polymerisation (Fig. 2) where as depolymerisation occurs when Cofilin, another ADF-H protein, removes ADP bound G-Actin from the '-' end of the filament (Hou et al. 2013). Capping proteins are employed at the '+' end to regulate the rate of polymerisation and COTL1 counteracts the activities of the capping proteins cap32/34 (Rohrig et al. 1995). Therefore by interfering with these proteins COTL1 indirectly promotes actin polymerisation (Hou et al. 2013; Liepinsh et al. 2004; Rohrig et al. 1995). The binding follows a 1:2 stoichiometry between COTL1 and actin and is a Ca^{2+} independent process (Rakonjac, 2009).

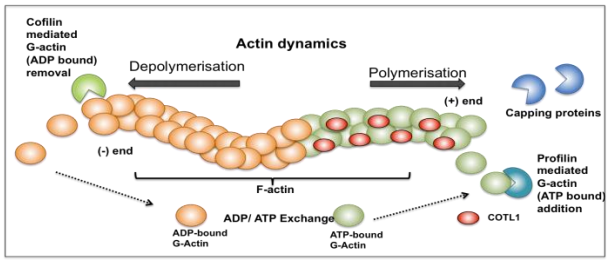

Figure 2: Schematic diagram showing the dynamic nature of F-actin.

ATP-G-actin is added on to the '+' end by Profilin, promoting actin polymerisation and ADP-G-actin is removed from the '-' end by Cofilin resulting in depolymerisation. COTL1 binds to F-actin at a 1:2 ratio, preventing binding of capping proteins, thereby promoting actin polymerisation.

This dynamic polymerisation-depolymerisation process enables F-actin to perform its functions involving cell migration and morphogenesis. Growth cones are structures that lead axons to synaptic targets by virtue of this process (Hou et al. 2013). Actin polymerisation drives the protrusion of lamellipodia and filopodia in the growth cones of axons (Gomez & Letourneau 2013). Therefore COTL1, which functions in actin polymerisation regulation, plays a critical role in neurite extension and neural crest migration (Hou et al. 2013). COTL1 was also found to be significantly involved in T-cell migration following CD28 stimulation (Kim et al, 2014). Suppression of COTL1 prevented lamellipodial protrusion at the T cell – B cell contact site owing to impaired T cell spreading in response to TCR ligation (Kim et al, 2014).

Role of COTL1 in Leukotriene synthesis

Both coactosin and COTL1 can bind to 5-LO to promote the formation of leukotrienes (LTs), lipid mediators that elicits inflammatory responses in allergic reactions, asthma and atherosclerosis (Funk, 2005). Since inflammatory reactions are part of cell defence mechanisms as well as chronic pathologies, it is imperative that regulation of 5-LO is a key step in maintaining the balance.

Any insult resulting in an increase in intracellular Ca^{2+} leads to the association of COTL1 to 5-LO in a 1:1 molar stoichiometry, prompting the translocation of the 5-LO-COTL1 complex to the perinuclear area (Fig. 3), where it docks to nuclear membrane phosphatidylcholine (PC) with the help of 5-LO activating protein (FLAP) (Esser et al. 2010; Liepinsh et al. 2004).

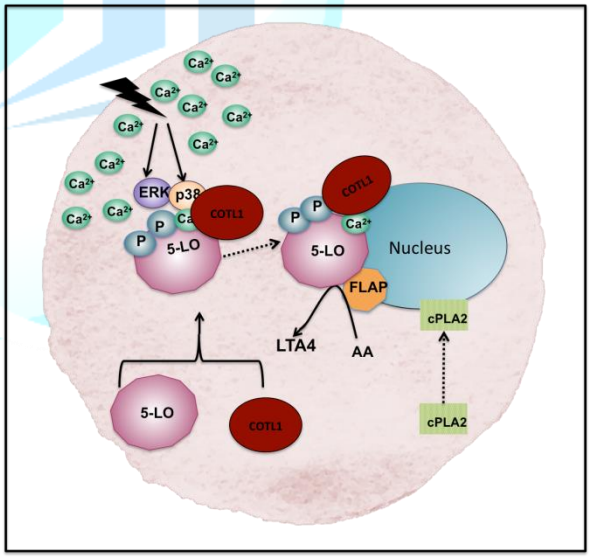

Figure 3: Schematic diagram showing 5-LO activation, translocation and LTA_4 synthesis in the cell.

A cellular stimuli leading to high intracellular Ca^{2+} or activation by MAP kinases ERK or p38 is thought to induce association of COTL1 with 5-LO. FLAP assists the translocation of the 5-LO- COTL1 complex to the nuclear membrane, where it converts AA to LTA4 (Adapted from Basavarajappa et al. 2014 and Rakonjac, 2009).

The enzyme cytosolic phospholipase A2 ($cPLA_2$), which is also translocated from cytosol to perinuclear area, releases arachidonic acid (AA) from PC, which is accessed by the 5-LO complex and converted into LTA_4 (Basavarajappa et al. 2014). 5-LO catalyses two initial steps in LT formation, the oxygenation of arachidonic acid to 5(S)-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) and the dehydration into epoxide. Thus, although 5-LO appears to be the initiator of the LT pathway, complete cellular 5-LO activity in presence of Ca^{2+}, including the nuclear translocation, was displayed only in presence of COTL1 and was absent in a COTL1 knockdown model (Basavarajappa et al. 2014). LTA_4 undergoes further enzymatic modifications to form either LTB_4 or cistenyl leukotrienes LTC_4, LTD_4 or LTE_4 (Rakonjac, 2009). Both LTB_4 and cistenyl leukotrienes have been found to induce monocyte chemo attractant protein 1 (MCP-1), a chemokine heavily involved in neuroinflammatory responses (Huang et al, 2004; Ichiyama *et al*, 2005). Taken together, these data invariably suggest the significance of 5-LO-COTL1 association in neuroinflammation and potentially neurodegeneration. In addition to increased intracellular Ca^{2+}, other stress stimuli causing an increase in p38 and ERK MAP kinase activation can subsequently phosphorylate 5-LO leading to its activation and ensuing LTA_4 production (Rådmark and Samuelsson, 2009).

Interaction of COTL1 with Organelles

There is a lack of research conducted on the direct interaction of coactosin and COTL1 on organelles outside of the cytoskeleton. However, there is an understanding on how cofilin, of which coactosin shares homology, interacts with mitochondria.

Cofilin plays a role in the regulation of mitochondrial action in apoptosis (Li et al, 2013). Apoptotic cell death is characterised by a distinct change in cellular architecture, demonstrated by blebbing of plasma membrane, externalization of phosphatidylserine, nuclear condensation and finally DNA fragmentation and release of cellular contents into circulation. Apoptosis occurs in three stages. The first is initiation in which a stress occurs that causes activation of one of various pathways to trigger a death signal that once sensed by the appropriate receptor leads to the second stage. The second stage is the commitment stage. Once a cell reaches this point the cell cannot reverse the process and will proceed to death. During this stage in apoptosis, apoptotic proteins interact with the mitochondria to permeabilise it to allow effectors, such as cytochrome c, to leave. Dephosphorylated Cofilin (Ser3) translocates from the cytosol to the mitochondria, and opens pores in the mitochondria to allow cytochrome c out, thereby playing a role in the commitment stage of apoptotic cell death (Li et al, 2013). Cytochrome c then forms a complex with activating factor-1 to cleave caspase-9, which activates Caspase-3. This step is considered part of the third stage of cell death, the execution stage, as it cleaves proteins that are essential to normal cell functioning. This leads to apoptosis resulting in cell death. It has also been shown that knockdown of cofilin leads to a reduction in the release of cytochrome c and hence apoptosis and cell death (Li et al. 2013; Li et al. 2015; Taha, Mullen & Obeid 2007).

Interaction of COTL1 with Sphingolipids

Sphingolipids are a class of lipids that contain a long chain sphingoid base (for example sphingosine). They can be found in mammalian plasma membrane and have been shown to play a role in a variety of cell signaling events including cell growth, cell death, cell differentiation and stress responses (Shayman 2000; Taha, Mullen & Obeid 2007).

Ceramides are a class of sphingolipids with a fatty acid linked to the amide group of the long-chain base. They serve as an intermediate for more complex sphingolipids such as phosphosphingolipids and glucosphingolipids. It has been proposed that ceramides play a role in signaling for programmed cell death based on two primary observations. The first is that agonists that induce apoptosis, such as CD95 and chemotherapeutic drugs, raise cellular levels of ceramide. The second is the artificial addition of cell permanent ceramides leads to an apoptotic response (de Chaves 2006).

There is evidence indicating the possibility that sphingolipids may play a role in neurodegenerative disorders. An increased level of ceramides has indeed been detected in the brain of Alzheimer's patients in early stages along with a reduced level of sulfatides in their brain grey and white matter and cerebrospinal fluid (Han et al, 2002). The elevated ceramide levels most likely arose from the breakdown of the sulfatides and can therefore be a potential biomarker for Alzheimer's (de Chaves 2006).

Due to the role of sphingolipids in the signalling of programmed cell death as well as its potential involvement in neurodegenerative disorders it is possible that COTL1 may interact with this biomolecule. An increase in COTL1 in endoplasmic reticulum fraction was in fact reported in lymphocytes isolated from Hereditary Sensory Neuropathy Type 1(HSN1) patients expressing V144D mutation in their serine palmitoyltransferase (SPT) long chain subunit 1 (SPTLC1) (Stimpson et al, 2016a). This increase in COTL1 was also further established in C133W, C133Y and V144D mutants in a neuronal cell model for HSN1 (Stimpson et al, 2016). SPT is a key enzyme involved in sphingolipid synthesis. The disease is characterised by degeneration of the dorsal root ganglion and presents with clinical onset from the second or third decades of the patient life (Stimpson et al, 2016b). Although the actual mechanism of COTL1 regulation is yet to be elucidated, its upregulation could be instigated by the increased oxidative stress upon the cellular cytoskeletal system, which can cause actin remodelling and potential axonal retraction in the neuron (Stimpson et al, 2016a). Increased COTL1 might also be triggering inflammatory pathways owing to its 5-LO binding property and subsequent LTA4 synthesis as described earlier. Whether COTL1 has any direct effects on sphingolipid metabolism or vice versa needs to be further investigated.

Currently there are very few other published reports on sphingolipid and COTL1 interaction. There is however one report that includes the interaction of a ceramide with coflilin-1 and F-actin in the stimulation of mouse embryonic stem cell migration (Park et al. 2013). The report indicates that the ceramide promoted the interaction between cofilin and F-actin to enhance mouse embryonic stem cell migration. This serves to further implicate a potential interaction between sphingolipids and COTL1.

The Role of COTL1 in Neurodegeneration

In Alzheimer's and other neurodegenerative disorders, inflammatory processes (such as the ones that COTL1 help to regulate) play a crucial role. 5-LO plays an important role in inflammatory responses, which are triggered by the presence of plaques such as in Alzheimer's patients. This results in activation of microglia and astrocytes leading to neuron cell degeneration and death. This can however cause worsening of the disease rather than healing it. Furthermore it has been shown that downregulation of 5-LO improves the memory and synaptic functioning in animal Alzheimer's models. Also there has been some epidemiological evidence that may suggest that anti-inflammatory treatment can have a positive effect in preventing or minimising the effect of Alzheimer's (Czapski et al. 2016).

Coactosin and COTL1 have ADF/cofilin homology. This family of proteins is essential in the formation of neurites via the organisation of

actin filaments (Sainath & Gallo 2015). For example cofilin increases actin depolymerisation and facilitates actin filament turnover as a way to regulate actin dynamics. Rods form spontaneously in neurons that overexpress ADF/cofilin, disrupting the microtubules. This does not cause cell death but does cause degeneration leading to a loss of synapses resulting in neurodegeneration (Minamide et al. 2000).

Cofilin aggregates and actin bundles have been observed in Alzheimer's brains. In low ATP environment (such as one caused by mitochondrial dysfunction or oxidative stress) there tends to be a higher ADP-actin and dephosphorylated cofilin concentration. Under these conditions the cofilin-actin complex readily forms into rods (neuropil thread structures). Rods that form as a result to this low ATP condition usually disappear shortly after, however in neurites with irreversible mitochondrial damage these rods become more permanent and can lead to loss of synaptic connections without loss of cells as mentioned above. This could be an explanation for the similar conditions that have been reported to occur in the early stages of neurodegenerative conditions (Maloney & Bamburg 2007; Whiteman et al. 2009).

Smith-Magenis syndrome (SMS) is caused by deletion of the short arm of chromosome 17. Its symptoms include neuro-behavioural abnormalities and congenital heart defects. The COTL1 gene is mapped to SMS common deletion region. This may indicate COTL1's involvement in the disease. The region also overlaps with a region associated with primitive neuro-ectodermal tumours. This suggests that COTL1 plays a role in DNA rearrangements of somatic cells (Nakatsura et al. 2002). Upregulated COTL1 expression has been identified in small cell lung cancer tissue thus suggesting it may be a biomarker or therapeutic target in these cancer patients (Jeong et al. 2010).

Conclusion

Neurodegenerative disorders are those that affect the normal functioning of the brain and its components. This occurs as a result of degradation of neurons including the formation of plaques and/or atypical protein assemblies. Despite being very common, very few of these disorders have a cure. As a result there is a large amount of research dedicated to understanding and finding cures or even early detection markers for these various diseases. One such example is the research conducted on the effect of COTL1 on neurodegeneration.

COTL1 being an actin binding protein plays a role in the maintenance of neuron structure, through its interaction with the cytoskeleton, and hence can potentially be involved in the loss of proper neuron structure leading to neurodegeneration. It is also involved in leukotriene synthesis for inflammatory responses, which can be triggered by plaques in patients suffering from these neurodegenerative disorders, and potentially worsens the condition. COTL1 shares homology with the ADF/cofilin family of proteins that play a role in mitochondrial apoptosis. This apoptotic effect can lead to unnecessary cell death in a low ATP environment and hence cause a large, unwarranted loss of neurons and/or the formation of neuropil thread structures, which can also lead to neurodegeneration. Furthermore sphingolipids also play a role in apoptosis and other important cell signalling events. The interaction between them and COTL1 may also be important in the triggering or control of neurodegeneration.

Currently there exists little research on the direct effect of COTL1 on neurodegeneration but what little there is does show promise in there being a link between the two. Subsequently more research needs to be conducted to further understand the connection, if any, between COTL1 and neurodegeneration.

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