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Review Paper

The cytoophidium: A novel intracellular compartmentation formed by metabolic enzymes

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ABSTRACT

Many enzymes are found to self-assemble into foci or fiber structure and these structures may play a complementary role except enzyme modification. Cytidine triphosphate synthase (CTPS), a vital metabolic enzyme that catalyses the rate limiting reaction of CTP synthesis, can form a filamentous structure termed cytoophidium. Although this structure is widespread and universally conserved across different organisms, the cytoophidium is heterogeneous. Also, it is still controversial whether they are enzymatic active and represent a functional assembly. Here, we briefly characterized the recent findings about the structure and potential function of cytoophidium. Furthermore, the regulatory mechanism of cytoophidium assembly/disassembly and the possible signaling pathway involved in CTPS synthesis were discussed. These findings might provide biomarkers prediction for tumors chemotherapeutic drugs and promote new translational medicine development.

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INTRODUCTION

Cellular compartmentation is a pivotal way to concentrate intracellular component that create a separate environment to regulate biochemical reaction and membrane-bound organelles in eukaryotic cell such as mitochondria, the best characterized example of compartmentation containing ATP synthase for energy storage and metabolic control. Recently, several studies identified some novel metabolic related organelles such as purinosomes (An et al., 2008), cytoplasmic processing bodies (P bodies) (Parker and Sheth, 2007) and uridine rich small nuclear ribonucleoprotein bodies (U bodies) can form highly-ordered aggregates without membranes. These filaments are markedly distinct from canonical cytoskeleton which are made up of either one or multiple metabolic enzyme complex either participating in the translational initiation or metabolic process. Continued investigation examining the crosstalk between U bodies and P bodies means a possible functional relationship between two organelles (Liu and Gall, 2007).

Williams et al. (1978) reported that CTPS activity increased in hepatomas, transplantable kidney tumors and primary renal cell carcinomas in human. Liu (2010) first found CTPS could form filamentous structure in *Drosophila* and the snake-like structure was termed cytoophidium. Only two months later, the other two groups reported the same phenomenon in bacteria and budding yeast, respectively (Ingerson-Mahar et al., 2010; Noree et al., 2010). Subsequently, many groups successively observed filamentous and ring structures contained CTPS in rat and human cells (Chen et al., 2011) indicating that cytoophidium is highly conserved in different organisms from prokaryotes to eukaryotes. The main component of this newly subcellular structure identified by fluorescence microscopy is a metabolic enzyme nucleotide CTPS which catalyzes the last and rate-limiting step of *de novo* CTP biosynthesis.

CTP is a fundamental building block that makes up the DNA and RNA involved in sialoglycoprotein synthesis and

served as an energy carrier. It is well known that adenosine-5-triphosphate (ATP) and uridine-5-triphosphate (UTP) are the substrates of CTP synthesis. GTP activating the glutamine hydrolyzed to generate ammonia is the rate limiting reaction in eukaryotes, while it uses ammonia directly as a nitrogen source in bacteria (Lieberman, 1956; Chakraborty and Hurlbert, 1961). Therefore, CTPS integrate all for nucleotide triphosphates in CTP synthesis reaction. CTPS mainly consist of two domains, a C-terminal glutamine-dependent aminotransferase (GATase) or glutaminase domain that deaminates glutamine and an N-terminal synthase (ALase) domain that uses UTP as substrate in an ATP dependent manner to synthesize CTP which comprises of the binding sites of these nucleotides (Goto et al., 2004; Kursula et al., 2006).

The activity of CTPS is activated by GTP mediated allosteric changes and ATP/UTP/CTP mediated tetramerization and repressed by CTP through competitive feedback (Pappas et al., 1998; Endrizzi et al., 2005; Levitzki and Koshland, 1972). Cytoophidium is represented as a novel frontier in the aspect of pyrimidine metabolism. In contrast to punctate or amorphous cytoplasmic bodies comprised of enzyme, a filamentous structure has advantage in greater surface area allowing for better enzyme activation. Conflict evidence was shown casting doubt on whether CTPS is the only component of cytoophidium, while CTPS from bacteria can self-assemble *in vitro*, making it possible that CTPS is the only component of cytoophidium. There exist incontinous gaps in the *Drosophila* through confocal microscopy indicating that some other components exist (Welte et al., 2016; Weichhart et al., 2008). Moreover, gene-wide screening of a collection of 4159 GFP-tagged ORFs verified twenty-three metabolic enzymes in *Saccharomyces cerevisiae* could also form filamentous structure and regulating translation initiation, glucose and nitrogen metabolism. These findings indicated that filament forming phenomenon may generally be observed with a functional regulation.

It is hypothesized that the formation of cytoophidium may serve as cytoskeletal elements and storage depot providing rapid reactivation enzyme under nutrient stress or regulatory roles. The exact mechanism by which CTPS is compartmentalized in a cell is still unclear.

In this review, an overview of the current knowledge of cytoophidium regulation is summarized. Further, we go on to elucidate the potential signaling pathway which may modulate the activity and formation of cytoophidium.

The morphology and function of cytoophidium

The filamentous structure of cytoophidium was spotted in cells across prokaryotes and eukaryotes and its morphology shows difference in number, length, polarity and localization. In human cells, CTPS incorporated into cytoophidia was not only found in cytoplasm but also in nucleus, moreover, both CTPS 1 and 2 possessed the ability to form filamentous structure. However, nuclear cytoophidia manifested different shapes as compared with cytoplasm cytoophidia and nuclear cytoophidia were mainly straight while cytoplasm possessed various morphology including curved, heart, ring-shaped and curled shapes. The length of cytoplasm seemed longer but thinner when compared to nuclear cytoophidia. Cytoplasm cytoophidia had sharp and blunt ends indicating a polarized characteristic like microtubulin (Gou et al., 2014).

Cytoophidium exists in all stages of cell cycle in human cells in contrast to other species and is distributed in the mid-plate and spindle at metaphase. In rat hippocampal neuron, the CTPS is highly spatial controlled distributed in axons but not in dendrites. CTPS cytoophidium, highly expressed in post-embryonic neuroblast and epithelial stem cells, is involved in brain development in *Drosophila* (Chen et al., 2011).

CTPS filament participates in oogenesis in *Drosophil.* The egg chamber is made up of 15 nurse cells, one oocyte and many somatic follicle cells surrounding the nurse cells and oocyte. Nearly every oocyte exhibits a cytoophidium. Two forms of CTPS filaments were observed in the cells: microcytoophidia and macrocytoophidia. Macrocytoophidia can be observed in the early and middle stages of oogenesis in follicle cells from stages 2 to 10, while only microcytoophidia appeared in stage 11. Macrocytoophidia is being considerably longer and thicker than microcytoophidia. In addition to occur in every cell types in the ovary, cytoophidia are also abundant in many tissues including lymph gland, testis, gut, trachea and accessory gland (Liu, 2010).

The appearance of cytoophidium in a wide range of organs questions whether it is a common way to regulate metabolism *in vivo*. Cytoophidia are enriched in the neuroepithelial stem cells in *Drosophila* optic lobes which is essential for optic lobe homeostasis (Tastan and Liu, 2015). Germline cells include a plethora of microcytoophidia correlated with golgi body marker actin-binding protein 2 (ABP2), raising the possibility that cytoophidia is involved in membrane phospholipid synthesis (Liu, 2010).

Bacterium, *Caulobacter crescentus* manifest curved morphology which is an excellent model for studying bacterial cytoskeleton. CreS was identified as a bacterial cytoskeleton protein localized to the inner cell curvature, while CTPS co-ordinate with CreS filament in regulating curved morphology with no relationship with its enzyme activity (Ingerson-Mahar et al., 2010).

In budding yeast *S. cerevisiae*, two CTPS encoding genes, Ura7p and Ura8p can colocalize and form foci or filament (Noree et al., 2010). It is still controversial whether Ura7p Colocalize with microtubule (Higgins et al., 2008). These

cytoophidia were shown straight and the average length of CTPS cytoophidia is about 2 to 3 μm. The assembly of cytoophidia includes five stages: nucleation, elongation, fusion, bundling, and circularization. The foci could elongate and fuse for many rounds by two types side by side fusion and head by head fusion to increase length and thickness respectively. Also, macro-cytoophidium could break apart into micro-cytoophidium (Gou et al., 2014). Hence, different forms of filament exist under certain conditions. The numbers of cytoophidia are apparently increased from exponential to stationary phases.

Cytoophidium assembly control and interaction

The occurrence of cytoophidium is sensitive to growth and nutrient conditions. CTPS filament may confine the active binding sites and disrupt the activity in response to the environmental stress. CTPS is released to the cytoplasm from cytoophidium and form active CTPS when stress is removed. Thus, cytoophidium formation is a method to store inactive enzyme and release them instantly in the case of nutrient needs to regulate metabolism. The mechanism by which enzyme assembles into large filament is still undefined. The assembly and disassembly of cytoophidium is also related to cell proliferation. There are many cytoophidia in *Drosophila* neural stem cells and mouse embryonic stem cells but disturbed when differentiation occurs, which means formation of cytoophidium is closely related to cell cycle entry or exit (Tastan and Liu, 2015).

Treatment of L-glutamine analog 6-diazo-5-oxo-L-norleucine (DON), a CTPS activity inhibitor through binding to its glutamine amidotransferase domain (GAT) substantially increased the length of cytoophidium (Chen et al., 2011; Levitzki et al., 1971). Another L-glutamine analog, azaserine has a similar effect in promoting cytoophidium formation. These data suggest that cytoophidium can be induced in limited nutrition such as glutamine deprivation and CTPS filament is inactive under this circumstance. However, CTPS formed in normal condition without starvation seems to obtain enzymatic activity (Strochlic et al., 2014). DON treatment also has different effect on cytoophidium assembly. DON promotes cytoophidium disassociate in bacteria *C. crescentus* whilst it promote cytoophidium formation in human and *Drosophila* cells (Ingerson-Mahar et al., 2010; Chen et al., 2011). Hence, cytoophidium appears heterogeneous under different conditions. This may be explained by the difference of species or DON exposure time.

The ubiquitination of CTPS is inversely related with CTPS filament formation. Immunoprecipitation results revealed a monoubiquitination modification which may regulate protein interaction instead of degradation (Pai et al., 2016). Autophagy can be induced by nutrient starvation and it is critical for cell survival. Cytoophidium is also resistant to autophagy-lysosome degradation in starvation. Thus, if the filament assemblies were not targeted for degradation and reversible upon growth recovery, it is likely that cytoophidium is a reservoir to store CTPS and become available upon cells exit from quiescence.

CTPS contains binding site of four nucleotides that either promote or inhibit enzyme activity and the filament length can be influenced by the sites mutation blocking CTP binding related to feedback inhibition and GTP binding corresponding to allosteric activation (Noree et al., 2014). CTPS cytoophidium was shown in an inactive dimmer form and transited to an active tetramer regulated by binding to ATP, CTP and UTP. UTP binding sites mutation that block tetramerization increase the frequency of filament but does not change the length of the filament indicating that tetramerization blocking influenced the nucleation stage but has little effect on the late fusion stage (Noree et al., 2014). E161 mutation blocked CTP binding to CTPS correlated with end product inhibition causing a corresponding increase in enzyme activity due to the loss of feedback inhibition by CTP completely eliminated filament assembly. Moreover, this mutation caused small foci but not filament suggesting that CTP binding blocking mainly influence the elongation and fusion stage of cytoophidium formation (Aughey et al., 2014; Barry et al., 2014).

In addition to allosteric interaction and feedback inhibition, other enzyme metabolic control such as phosphorylation was observed in *Drosophila* cytoophidia (Liu, 2010). Many phosphorylation sites have been shown to regulate enzyme activity (Yang and Carman, 1996; Tumaneng et al., 2012; Park et al., 2003).

Destabilization of tetramer or blockade of the catalytic activity accelerates CTPS filaments formation in *S. cerevisiae* indicating that CTPS filament is composed of inactive dimmer and become an active tetramer when binded to ATP, CTP or UTP (Noree et al., 2014), whereas it was observed that the repeating sub-units of CTPS filaments purified from *Escherichia coli* are X-shaped tetramers observed by cyto-electron microscopy (Barry et al., 2014). Although widely observed in various species, cytoophidium formation shows different regulations. The relationship between CTPS enzyme activity and filament formation were further examined by novel light-scattering and absorbance assay. The polymerization of CTPS is apparently attenuated through elevating CTP concentration. Whether CTPS synthase incorporated into cytoophidia is active or exists with both active and inactive need to be further elucidated.

The regulatory protein of cytoophidium assembly

The regulation mechanism of CTPS enzyme activity and cytoophidium formation is only with a few examples. Here, we listed the current findings on proteins regulate the morphology and enzyme activity of cytoophidium.

Ack kinase

The assembly of CTPS is regulated by non-receptor tyrosine kinase DAck, the *Drosophila* homologue of mammalian Ack1 (activated cdc42-associated kinase 1), DAck colocalized with CTPS in germline cells of egg chambers from flies and mutation of DAck disassembled CTPS filament architecture and morphological defects which is correlated with reduced fertility (Strochlic et al., 2014).

Cbl

Proto-oncogene Casitas B-lineage lymphoma (Cbl) plays a role in endoreplication controlling cytoophidium structure. Disruption of Cbl function not only influences the process of cytoophidium formation, but also the subsequent reduction of S-phase events. Cbl as an E3 ligase is critical for the stabilization of cytoophidium assemble in *Drosophila* follicle cells in endocycle. Pai et al. (2016) further examined the functional role of ubiquitin modification system performed in CTPS filament using the proteasome inhibitor, MG132 disassembled cytoophidium in *Drosophila* follicle cells; the length of cytoophidium was shortened in the nurse and oocyte cells. This phenomenon could be reversed by over-expression of ubiquitin. Despite the essential role of ubiquitin for cytoophidium formation in *Drosophila* S2 and human epithelial type 2 cell line (HEp-2, a HeLa derivative cell) with deprivation of glutamine or serum. The ubiquitination of CTPS is inversely related with CTPS filament formation. Immunoprecipitation results revealed a monoubiquitination modification which may regulate protein interaction instead of degradation.

Myc

The formation of cytoophidium is in keep with the expression of Myc from early oogenesis to mid-oogenesis in *Drosophila* follicle cells; the cytoophidia and Myc was down-regulated during late oogenesis. c-Myc is also an oncogene and proposed to increase in many cancers, while the expression of CTPS are upregulated in many forms of cancer such as hepatomas and colon cancer (Azzam and Liu, 2013). The similar expression pattern of Myc and CTPS implicate the functional relationship between them, while ChIP-seq validated the c-Myc binding sites at the CTP locus. Myc over-expression promotes cytoophidium assembly, while Myc RNAi disrupts cytoophidium formation. Myc is shown to be an organ size regulator in *Drosophila*. CTPS knockdown significantly decreased the cell size in nuclear areas that over-expressed Myc, whilst only altering CTPS expression in normal myc activity has no such phenomenon (Noree et al., 2014). If this is the case, CTPS will be a fascinating therapeutic strategy in Myc-dependent cancers.

In addition to CTPS, Myc induced many metabolic genes like PPAT, DHODH, IMPDH1 and IMPDH2. ChIP-PET experiment also identified CTPS bind to E-box or PET clusters in close proximity to the transcriptional start site of many nucleotide metabolic genes which implicate Myc may activate purine biosynthesis except pyrimidine biosynthesis (Liu et al., 2008).

Inosine 5[prime]-monophosphate dehydrogenase (IMPDH)

Recent studies indicated that CTPS catalyzed the first and rate limiting reaction for the synthesis of CTP nucleotide, while IMPDH catalyzed the NAD-dependent oxidation of inosine monophosphate (IMP) to xanthosine monophosphate, the first and rate limiting step of GTP synthesis. Two isoforms of IMPDH were found in humans including IMPDH1 and IMPDH2. Colocalization study visualized both CTP and IMPDH enriched in filamentous rods and rings structure despite they regulate different nucleotide synthesis pathway (Keppeke et al., 2015).

Previous study demonstrated that mycophenolic acid (MPA), an uncompetitive inhibitor of IMPDH activity induced the formation of filament in an inactive form similar to the CTPS cytoophidia in inhibiting enzyme activity (Carcamo et al., 2011). It is still unknown whether they interact directly or bind to a scaffold protein. However, many laboratories argued that CTPS and IMPDH cytoophidia exist independently, partly or fully colocalized in mammalian cells. Inhibition of cell growth through suppression of PI3K-Akt-mTOR pathway triggers IMPDH disassemble in mouse fetal liver cell line BNL CL2, while CTPS cytoophidia usually assemble in the limit nutrition. Moreover, IMPDH cytoophidia formed in mouse are freshly isolated islet cells *in vivo* related with insulin secretion (Chang et al., 2015). The purine and pyrimidine synthesis share the common substrate PRPP (5-phosphate-α-D-ribosl 1 pyrophosphate) and inhibition of pyrimidine may activate purine synthesis as evidenced by restriction of CTP synthesis triggered by IMPDH filament formation.

CTPS filament synthesis and signal pathway

mTOR signaling and CTPS filament synthesis

The pathway regulating cytoophidium assembly is still unknown and cytoophidium is usually formed in a starved condition for storing metabolic enzyme. The mechanistic/mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine kinase which is a member of the PI3K related kinase (PIKK) family. mTOR consists of two distinct complexes known as mTOR

complex 1 (mTORC1) and mTORC2 distinguished by the scaffold protein raptor (regulatory associated protein of mTOR) and rapamycin-insensitive companion of mTOR (Rictor). mTORC1 is a growth signal sensor regulating cellular growth and proliferation and is also sensitive to the nutrient stress which may participate in mediating cytoophidium assembly. Here, we summarized the recent findings about how mTOR signaling affects nucleotide synthesis and other filamentous structure which may provide some clues to the potential pathway involved in cytoophidium assembly.

mTOR signaling in nucleotide synthesis

The evolutionarily conserved mTOR is an essential sensor of growth and nutrient signal controlling several metabolic processes (Dibble and Manning, 2013). The mTORC1 can be inhibited by rapamycin. The eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BPs) and the ribosomal S6 kinases (S6Ks) 1 and 2 are two main mTORC1 substrates shown to modulate protein synthesis (Yang et al., 2013). mTORC1 facilitate the gene transcription including de novo lipogenesis, glycolysis and pentose phosphate pathway (PPP) (Duvel et al., 2012). Growth factors and hormones activate mTOR through PI3K/Akt and Ras/mitogen-activated protein kinase (MAPK) pathways. Since many proteins in this pathway are oncogenes or tumor suppressors, the mutation or abnormal expression of these proteins result in abnormal mTORC1 signaling in most human cancers (Menon and Manning, 2008; Laplante and Sabatini, 2012).

mTOR signaling promote de novo pyrimidine synthesis in response to growth factors and amino acids through its downstream substrate S6K1, which stimulate CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotatase), the protein containing three different enzymes that catalyzes the first three steps of de novo pyrimidine synthesis to form a pyrimidine ring through phosphorylates at S1859. The enzyme mTORC1 also have an effect on the late step of pyrimidine synthesis through delayed enhancement of pentose phosphate pathway (Robitaille et al., 2013). In addition to impact the initial step of pyrimidine synthesis, mTORC1 also promote PRPP production required for the late step of pyrimidine synthesis and stimulate the synthesis of purine nucleotides through ATF4-dependent transcriptional induction of the mitochondrial tetrahydrofolate (mTHF) cycle (Ben-Sahra et al., 2016).

mTOR signaling and purinosome synthesis

It was first reported that six enzymes of de novo purine synthesis reaction were able to assemble in a complex in the cytoplasm (An et al., 2008). Many proteins were reported to affect the assembly of purinosome including casein kinase II (CK2), heat shock protein, Hsp-90 and Hsp-70 and GPCR. However, little is known about the signaling pathway of purinosome. It was also observed that 3-phosphoinositide-dependent protein kinase 1 (PDK1) was involved in regulating purinosome assemble but not disassemble in mammalian cells. None of Protein kinase C (PKC), Akt (serine/threonine-specific protein kinase, also called protein kinase B) and mTOR, the downstream kinase of PDK1 influenced purinosome formation. Recently, Fang et al. (2016) identified that purinosome could colocalize with mitochondria through a super resolution fluorescence imaging method, while purinosome is a multi-enzyme complex involved in the de novo purine biosynthesis; they purified mitochondria and using mass spectrometry identified adenylosuccinate lyase (ASL or ADSL) interact with mitochondria. Physical interactions led them further to investigate the functional relationship between purinosome and mitochondria.

Inhibition of mitochondria electron transport or metabolism increased the purinosome content indicating a close relationship between purinosome metabolism and mitochondria function. mTOR is an important regulator of cellular metabolism involved in regulating mitochondria function and nucleotide. Using mTOR inhibitor disrupts the purinosome assembly and colocalization with mitochondria indicating that mTOR plays a synergy role in regulating nucleotide metabolism and mitochondria function in order to respond to the nutrient requirements.

Glul filament formation and hippo signaling pathway

The characteristic of cytoophidium is heterogeneous in different species and as such we proposed that more than one signaling pathway may participate in glul filament formation. The hippo pathway is crucial for precisely controlled organ size and tissue regeneration. A key downstream effector of the hippo signaling pathway is YAP which is important for regulating proliferation and apoptosis (Zhao et al., 2011). Recently, Cox et al. (2016) verified that Yap is involved in glutamine metabolism though elevating glutamine synthetase (glul) expression and activity. Glul can form filament and that filament assembly can also trigger to enzyme inactivation in starvation in budding yeast. Such characteristic is similar to CTPS filament indicating that enzymatic filament formation is a general mechanism to store enzymes in response to limited nutrient (Petrovska et al., 2014). There is need for further investigation regarding the influence of Hippo-Yap signaling pathway on the assembly of Glul/CTPS filament. mTOR pathway also crosstalk with other pathways and the increase of cell size induced by Yap could be disturbed by rapamycin indicating that Yap facilitate cell growth through mTORC1 (Tumaneng et al.,2012).

Conclusions

To date, with the improvement of genetic screening and microscopic approaches, the structure and assembly of cytoophidium have been extensively elucidated. Cytoophidium is dynamic and undergoing structure swift in response to environmental change. Further mining of data in more specific condition may provide more useful data. Cytoophidium utilizes polymerization-mediated strategy supposed to be involved in regulating cytoskeletal elements, storage enzyme for rapid reactivation. To generate one or many mutations by using CRISPER/Cas9 technique studies the biology of cytoophidium and the mechanisms of heterogeneity between different species. Whether assemble of metabolic enzyme into cytoophidium is a strategy for cell survival similar to autophagy need more evidence. Large-scale chemical screening of 2000 compounds have identified CTPS inhibitors acivicin, a glutamine analogue, regarded as a useful anti-proliferative drug in a *Drosophila* metastatic tumor model (Willoughby et al., 2013). CTPS has been presumed as an attractive drug targets against viral and parasite disease, malaria, and infectious blindness. However, the relationship between cytoophidium assembly and cancer metabolism still undefined. Deeper understanding of the molecular pathway mechanism by which cytoophidium formation are regulated may better understanding the role of cytoophidium in metabolism.

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