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Review

Membrane lipid compositional sensing by the inducible amphipathic helix of CCT

Rosemary B. Cornell

Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, B.C. V5A 1S6, Canada

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ABSTRACT

The amphipathic helical (AH) membrane binding motif is recognized as a major device for lipid compositional sensing [1]. We explore the function and mechanism of sensing by the lipid biosynthetic enzyme, CTP:phosphocholine cytidylyltransferase (CCT). As the regulatory enzyme in phosphatidylcholine (PC) synthesis, CCT contributes to membrane PC homeostasis. CCT directly binds and inserts into the surface of bilayers that are deficient in PC and therefore enriched in lipids that enhance surface charge and/or create lipid packing voids. These two membrane physical properties induce the folding of the CCT M domain into a ≥60 residue AH. Membrane binding activates catalysis by a mechanism that has been partially deciphered. We review the evidence for CCT compositional sensing, and the membrane and protein determinants for lipid selective membrane-interactions. We consider the factors that promote the binding of CCT isoforms to the membranes of the ER, nuclear envelope, or lipid droplets, but exclude CCT from other organelles and the plasma membrane. The CCT sensing mechanism is compared with several other proteins that use an AH motif for membrane compositional sensing. This article is part of a Special Issue entitled: The cellular lipid landscape edited by Tim Levine and Anant K. Menon.

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1. Metabolic and biophysical rationale for lipid compositional sensing by CCT

1.1. CCT is the regulatory enzyme for PC synthesis, and a prototypical amphitropic protein

In most eukaryotic cells CCT catalyzes the key rate-limiting step in the major pathway for PC biosynthesis, the synthesis of the phosphocholine headgroup donor, CDP-choline [2]; (Fig. 1A). Membrane PC homeostasis is essential for maintaining optimal membrane physical properties such as impermeability, intrinsic curvature stress, surface electrical potential and ultimately, biological function. CCT, working in concert with PC-directed phospholipases, provides a control mechanism for maintaining PC homeostasis [3]. CCT can sense the PC content of membranes and can transform a physical signal on the membrane surface into a change in enzyme activity and CDP-choline production to regulate PC content. This review attempts to explain how the enzyme recognizes a membrane binding site, how it changes conformation to interact with that site, and how that interaction and new conformation trigger catalytic function.

CCT binds weakly and reversibly to cell membranes, and is active only when membrane-bound, a property sometimes referred to as amphitropism [4–7]. Although hundreds of proteins share this property, CCT was one of the first enzymes shown to be regulated by reversible membrane translocation in both cells and in vitro [8–11]. Table 1 lists some of the agents or conditions that modulate PC synthesis in cells by changing the membrane partitioning of CCT. CCT isolated from the soluble fraction of cells was inactive unless lipids, usually in the form of sonicated vesicles, were provided [12,13], indicating that it is a lipid-dependent enzyme. The enzyme was not activated by pure PC vesicles, but when incorporated into PC vesicles a diverse set of minor lipid species, discussed in depth in Section 3, could do the trick. Extensive molecular analyses have identified a long membrane-inducible amphipathic α-helix (AH) in the regulatory region as the domain responsible for lipid compositional-sensing and membrane-binding [14–17]. The AH domain, also known as domain M, is located C-terminal to the catalytic domain (Fig. 1B), and is followed by an acidic and/or ser-pro-rich disordered tail. When membrane bound the long axis of the AH is parallel to the membrane surface. Domain M is auto-inhibitory in the enzyme's soluble form and activating in the membrane bound form. Table 2 provides examples of amphitropic proteins that like CCT use amphipathic helices as membrane-binding domains, along with membrane recognition features. There are principally two physical features

Abbreviations: AI, auto-inhibitory; AH, amphipathic helix; CCT, CTP:phosphocholine cytidylyltransferase; CD, circular dichroism; CCT_{sol}, soluble form of CCT; CCT_{mem}, membrane-bound form of CCT; DAG, diacylglycerol; TAG, triacylglycerol; $iPLA_2$, calcium-independent PLA_2; LD, lipid droplets; NE, nuclear envelope; NLS, nuclear localization signal; PC, phosphatidylcholine; PA, phosphatidic acid; PE, phosphatidylethanolamine; PS, phosphatidylserine; PG, phosphatidylglycerol; PIP_2, phosphatidylinositol 4,5-bisphosphate; PM, plasma membrane; SUVs, small unilamellar vesicles; MLVs, multilamellar vesicles.

E-mail address: cornell@sfu.ca.

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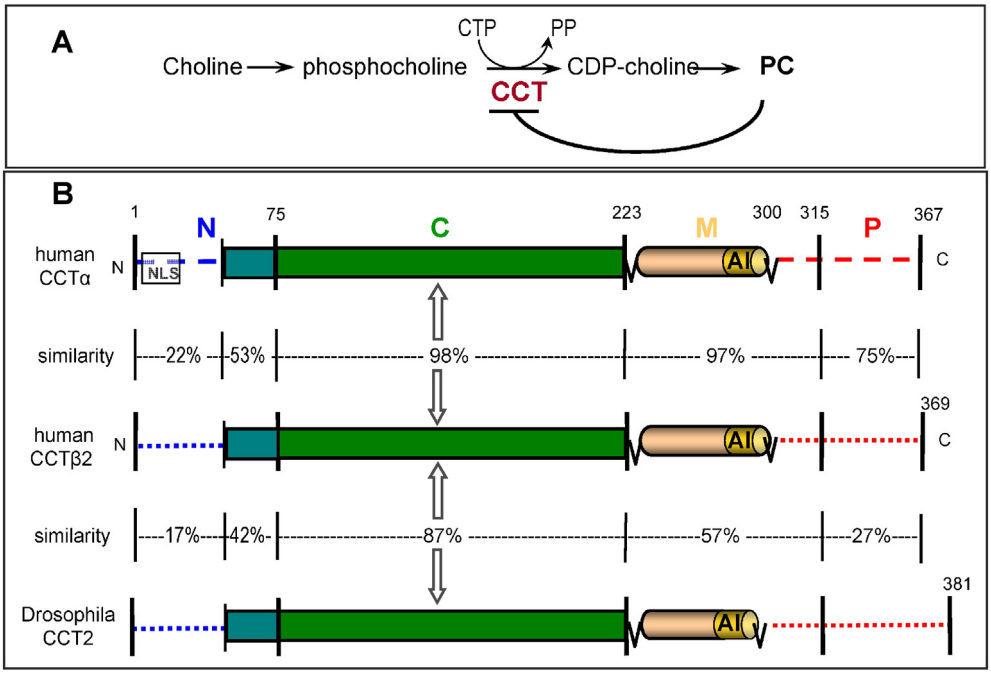

Fig. 1. A. CDP-choline pathway for PC synthesis, showing feedback regulation by the pathway end-product, PC. B. Domain structure of representative CCTs. Disordered N-terminal segment of variable length is followed by the N-Cap segment (teal) of ~35 residues that is known to form an ordered structure on the "top" of rat CCTa catalytic domain (domain C). Domain C (green) is a highly conserved ~150 residue α/β fold, and is followed by variable-length domain M (beige, with the auto-inhibitory (AI) helix indicated in gold). When membrane-bound domain M forms a continuous AH with approximate boundaries as shown. The disordered P segment is also of variable length and low sequence conservation.

of the membrane that can be recognized by an AH motif: surface negative charge density and surface packing defects. As most AH motifs are electrically positive, the membrane negative charge serves as an attractant, and the packing defects provide insertion sites for the non-polar face of the helix. Table 3 lists the membrane recognition features specific for CCT that will be discussed in depth in this review.

1.2. CCT responds to a PC-deficient bilayer by membrane partitioning (translocation)

CCT localization and function in a cell are largely governed by a partitioning equilibrium between soluble and inactive versus membrane-bound and active CCT (Fig. 2). What factors regulate this equilibrium? Membrane partitioning and activation of CCT in cultured cells accompany treatments that are predicted to decrease the membrane PC content relative to other phospholipids and/or increase the content of PC catabolites [18–21]; see Table 1 for a partial list. For example, phospholipase C treatment degrades PC into diacylglycerol (DAG), and triggers CCT translocation [10,22]. Choline deficiency generates a decrease in PC relative to PE, and leads to CCT translocation [23,24]. Treatments that elevate the content of minor lipid species such as free fatty acid, or phosphatidic acid (PA) also promote CCT-membrane binding [25–28]. Importantly, CCT catalytic efficiency can be increased more than 200-fold upon binding to pure lipid vesicles in the absence of any other protein components [29,30], suggesting that the partitioning and activation in cells is a lipid-driven process.

To make sense of these observations a PC metabolic cycle has been put forward in which enhanced catabolism triggers enhanced synthesis and vice versa. Lipid catabolites of PC such as DAG, PA, and free fatty acids promote membrane binding of CCT and enzyme activation to speed up PC synthesis and re-utilization of these bilayer-disrupting lipids [20,21,31]. There is much evidence in support of this model. For example, phorbol ester treatment led to activation of phospholipases resulting in DAG production and stimulation of CCT activity and PC synthesis [32]. The build-up of DAG and fatty acid was transient, as PC synthesis utilizes these precursors [33–35]. In several mammalian cell lines agonist-induced phospholipase D (PLD) activity was coupled to CCT translocation and/or activation [36,37]. When PA, the direct product of PLD action on PC, was elevated in *Arabidopsis thaliana* (by preventing its conversion to DAG) a ~3-fold activation of CCT ensued [26], showing a CCT response to a PC catabolite in cells. This model is also supported by direct activation of CCT in vitro by lipid vesicles that contain the PC catabolites, DAG, PA, or fatty acids (see Sections 3.1, 3.2). There is also evidence that PC catabolic enzymes are sensitive to CCT activity and PC synthesis rates to maintain PC homeostasis [3,20,21]. When CCT expression was elevated by transfection of COS-1 cells, PC synthesis was accelerated 3 to 5-fold, but a countervailing increase in PC turnover resulted in only a small accumulation of PC in these cells [35]. Similarly when CCT translocation was stimulated by oleic acid treatment of Krebs-II ascite cells, PC

Table 1
CCT amphitropism: correlations with altered lipid composition and phosphorylation status. The conditions highlighted in green stimulate PC synthesis. Those highlighted in orange inhibit PC synthesis. No Δ, indicates no change was observed. Empty boxes indicate no measurement reported [191–206].

Conditions that alter PC synthesis	Membrane partitioning	Lipid compos–itional change	CCT phos–phorylation	References
phospholipase C	↑	↓PC; ↑ DAG	↓	(10, 191, 192)
Phorbol ester	↑	↑ DAG	No Δ	(10, 32, 191–194)
Fatty Acid	↑	↑ Fatty acid	↓	(8, 25, 56, 195, 196)
Diacylglycerol (DiC8)	↑	↑ DAG		(32, 191, 197)
Go → G1 transition	↑	↑ DAG, ↑ Fatty acid	↓	(40, 67, 198)
NGF	↑			(199)
Serum	↑	↑ DAG, fatty acid, PA	↓	(40, 67)
Angiotensin II	↑	↑ DAG, ↑ Fatty acid	No Δ	(200, 201)
Farnesol	↑	↑ Farnesol		(202)
Fatty–acid feeding/lipogenesis	↑	↑ fatty acid; ↑ TAG		(71, 101)
Choline deficiency[a]	↑	↓PC; ↑ PE	↓	(23, 203)
Alkyl phosphocholine and related compounds	↓	↑ lyso–lipids		(42, 128, 204)
Okadaic acid	↓		↑	(205)
Oxysterol/retinoic acid			↑	(206)

[a]Although choline deficiency induces CCT binding to membranes, PC synthesis was not increased due to lack of choline substrate.

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