Progress in Lipid Research 59 (2015) 147–171

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

CTP:phosphocholine cytidylyltransferase: Function, regulation, and structure of an amphitropic enzyme required for membrane biogenesis

Rosemary B. Cornell [a,*], Neale D. Ridgway [b]

[a] Department of Molecular Biology and Biochemistry and the Department of Chemistry, Simon Fraser University, Burnaby, B.C. V5A-1S6, Canada
[b] Departments of Pediatrics, and Biochemistry and Molecular Biology, Atlantic Research Centre, Dalhousie University, Halifax, Nova Scotia B3H-4H7, Canada

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 7 July 2015
Accepted 7 July 2015
Available online 9 July 2015

Keywords:
Phosphatidylcholine metabolism
Isoform functions
Membrane translocation
Amphipathic helix
Lipid activators
Auto-inhibitory domain

ABSTRACT

CTP:phosphocholine cytidylyltransferase (CCT) catalyzes a rate-limiting and regulated step in the CDP-choline pathway for the synthesis of phosphatidylcholine (PC) and PC-derived lipids. Control of CCT activity is multi-layered, and includes direct regulation by reversible membrane binding involving a built-in lipid compositional sensor. Thus CCT contributes to phospholipid compositional homeostasis. CCT also modifies the curvature of its target membrane. Knowledge of CCT structure and regulation of its catalytic function are relatively advanced compared to many lipid metabolic enzymes, and are reviewed in detail. Recently the genetic origins of two human developmental and lipogenesis disorders have been traced to mutations in the gene for CCTα.

Contents

Abbreviations: AI, auto-inhibitory; CCT, CTP:phosphocholine cytidylyltransferase; CCT_{sol}, soluble form of CCT; CCT_{mem}, membrane-bound form of CCT; CT, cytidylyltransferase; ECT, ethanolamine-phosphate cytidylyltransferase; ERK, extracellular signal-regulated kinase; GCT, glycerol-phosphate cytidylyltransferase; IAA, indol acetic acid; LPS, lipopolysaccharide; iPILA2, calcium-independent PLA2; PC, phosphatidylcholine; PA, phosphatidic acid; DAG, diacylglycerol; m-AH, membrane-induced amphipathic helix; UPR, unfolded protein response; PEMT, PE N-methyltransferase; PLA2, phospholipase A2; PE, phosphatidylethanolamine; PS, phosphatidylserine; PIP_2, phosphatidylinositol 4,5-bisphosphate; LDs, lipid droplets; NE, nuclear envelope; NR, nucleoplasmic reticulum; NLS, nuclear localization signal; NES, nuclear export signal; HDL, high density lipoproteins; VLDL, very low density lipoproteins; CHO, Chinese Hamster Ovary; MAP, mitogen-activated protein.

* Corresponding author.
E-mail address: cornell@sfu.ca (R.B. Cornell).

http://dx.doi.org/10.1016/j.plipres.2015.07.001
0163-7827/

1. Introduction

1.1. CCT plays a pivotal role in phospholipid metabolism

Phosphatidylcholine (PC) is a major phospholipid component of the membranes of most nucleated cells. PC abundance can range from <15% of total phospholipids in myelin plasma membrane to >60% in rat liver ER [1]. PC is also a major component of phospholipid monolayers of serum lipoproteins, lung surfactant, and lipid droplets. It is the major phospholipid component of bile micelles. PC is a source of lipid second messengers such as diacylglycerol (DAG), phosphatidic acid (PA) and arachidonic acid [2], and is the biosynthetic precursor to other membrane phospholipids, including sphingomyelin, phosphatidylethanolamine (PE), and phosphatidylserine (PS) [3]. PC can also serve as a fatty acid donor for diacylglycerol conversion to triacylglycerol [4,5]. Lastly it serves as the source for glycerophosphocholine, the non-lipid osmolyte which has critical function in kidney and neural cells [6].

CCT catalyzes the key rate-limiting step in CDP-choline pathway for PC biosynthesis (Fig. 1), and together with phospholipases, is considered to be responsible for PC homeostasis. Nature has evolved elaborate mechanisms to control the phospholipid composition of membranes, which influences their intrinsic curvature, elasticity, viscosity, surface electrical potential and, ultimately, biological function. CCT provides one of these control mechanisms by virtue of its ability to 'sense' or 'survey' the PC content of membranes and convert this physiochemical signal to a change in enzyme activity and CDP-choline synthesis that regulate PC content.

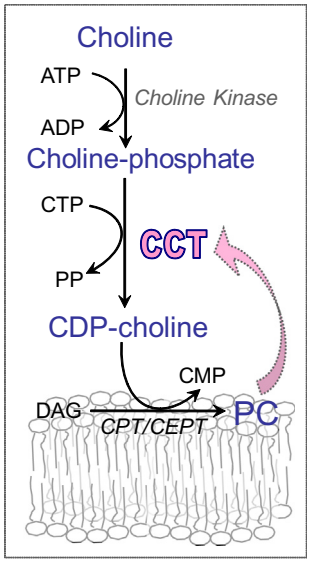

Fig. 1. CDPcholine pathway for PC synthesis. Choline is imported through one of several transporters [252,271] phosphorylation by choline kinase occurs in the cytoplasm. CCT catalyzes the rate-limiting step in most cellular states and its activity is regulated by signals from the membrane (pink arrow) that report on the relative PC abundance. Upon translocation of CCT to the membrane CDP-choline is converted to PC via the activity of a dedicated CDP-choline phosphotransferase (CPT) or a dual-function CDP-choline/ethanolamine phosphotransferase (CEPT).

1.2. PC synthesis sustains membrane homeostasis and cell division

Cells that are active in growth, secretion, differentiation or cell division need to produce sufficient membrane components to conserve or augment mass, and to replace the degraded components. Differentiation is often accompanied by net membrane expansion, for example in adipogenesis or B cell differentiation into antibody-secreting cells [7]. Secretory vesicles are highly dynamic as they shuttle cargo out of the cell from the endoplasmic reticulum (ER), engulf extracellular material and recycle back to the surface after processing. The high rate of metabolic turnover of membrane components during these processes produces lipid mediators that may be required for optimal vesicular traffic [6,8,9]. The CCT contribution to PC supply in a variety of secretion systems is discussed in Section 2.3.