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Review

The role of choline in prostate cancer

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ABSTRACT

Choline is an essential nutrient that is necessary for cell membrane synthesis and phospholipid metabolism and functions as an important methyl donor. Multiple roles for choline in cancer development have been suggested. Choline can affect DNA methylation and lead to a disruption of DNA repair. It can also modify cell signaling that is mediated by intermediary phospholipid metabolites, and it can support the synthesis of cell membranes and thus support cell proliferation. A higher intake or status of choline in plasma and tissues has been related to higher cancer risks. Prostate cancer shows elevated levels of choline uptake and levels of certain choline metabolites. Choline metabolites can be used as potential prognostic biomarkers for the management of prostate cancer patients. Targeting certain enzymes, which are related to choline metabolism, provides promising therapeutic opportunities for tumor growth arrest. This review summarizes the potential role of choline metabolism in cancer, especially in prostate cancer.

Contents

Introduction

Choline is an essential nutrient [1]. The main dietary sources of choline are beef and chicken liver, eggs, wheat germ, and dried soybeans [2]. The recommended daily requirements for choline have been set to 550 mg/day for men and 425 mg/day for non-pregnant women [1]. Choline is necessary for the synthesis of acetylcholine, membrane and signaling phospholipids, and as a source of methyl groups [3].

Dietary intake is not the only source of choline, since a considerable amount of this compound can be produced de novo from phosphatidylethanolamine via phosphatidylcholine (PtdCho). Pathological changes in the liver and muscles were observed in 77% of men on a diet that was poor in choline [4]. These observations suggest that the endogenous synthesis of choline is not sufficient to meet the daily requirements. Genetic variations of choline dehydrogenase and phosphatidylethanolamine *N*-methyltransferase can influence the dietary requirements for choline [5,6].

Choline metabolism has been linked to malignant transformation characterized by a higher proliferation rate and increased phosphocholine (PCho) and other choline-containing compounds [7,8]. Inducing the proliferation of normal cells by growth hormones was not

Abbreviations: CCT, CTP-phosphocholine cytidylyltransferase; CDP-Cho, cytidine diphosphate choline; CHK, choline kinase; CHTs, high-affinity choline transporters; CPT1, diacylglycerol cholinephosphotransferase 1; CTLs, choline transporter-like proteins; CTP, cytidine triphosphate; DAG, diacylglycerol; Eth, ethanolamine; GPC, glycerophosphocholine; GPC-PDE, glycerophosphocholine phosphodiesterase; GPE, glycerophosphoethanolamine; Lyso PLA1, lyso-phospholipase A1; OCTs, organic cation transporters; OCTNs, organic cation/carnitine transporters; PEth, phosphoethanolamine; PCA, prostate cancer; PCho, phosphocholine; PLA2, phospholipase A2; PLC, phospholipase C; PLD, phospholipase D; PtdCho, phosphatidylcholine.

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associated with an increase in PCho and total choline levels in one study [8]. Therefore, the role of choline in cancer goes beyond the expected higher requirements caused by cell division and the increased synthesis rate of new cell membranes. Cancer cells exhibit an abnormal choline phospholipid metabolism [8–10]. The extensive alterations in choline metabolism in malignant transformation have been shown to be related to the expression of enzymes involved in this pathway [7]. Moreover, aberrant choline metabolism might be related to malignant transformation via genetic and epigenetic dysregulations [11,12].

Few studies observed a positive association between the dietary choline intake or plasma concentration of choline and the risk of some types of cancer [13,14], including PCA [15]. Other studies observed no significant relationship [16,17]. Prostate cancer (PCA) accounts for 14% of all newly diagnosed cancer cases worldwide in 2008 [18]. The rising incidence rate of PCA reflects in part the widespread screening for prostate-specific antigen (PSA). Risk factors such as age, ethnicity, family history, lifestyle, and androgens are also discussed in relation to the PCA risk [19,20]. Beyond enhanced lipid biosynthesis, altered choline phospholipid metabolism is one of the characteristic features of PCA [21,22]. Dietary choline, as a major source of choline, phospholipids, and methyl groups might be a potential modifiable risk factor or risk marker for PCA.

The role of choline phospholipid metabolism in cell function and signaling makes it one important target candidate for tumor treatment or prevention. This review summarizes the current knowledge regarding the implications of choline in carcinogenesis and discusses the potential usage of choline and choline phospholipid metabolites as prognostic biomarkers in patients with PCA.

The role of choline as a methyl donor

The proportional distribution of dietary or endogenous choline between phospholipids and the methylation pathways has not been studied much. Choline is oxidized to betaine via two-step irreversible reactions mediated by choline dehydrogenase and betaine aldehyde dehydrogenase. Betaine homocysteine methyl transferase mediates the transfer of the methyl group from betaine to homocysteine to produce methionine that is in turn converted into S-adenosylmethionine (SAM), the universal methyl donor (Fig. 1). Choline is utilized to generate the methyl group required for phospholipid metabolism. The SAM-dependent phosphatidylethanolamine *N*-methyltransferase catalyzes the methylation of phosphatidylethanolamine (PtdEth) to PtdCho, an important source for the de novo synthesis of choline [3,23].

Epigenetic mechanisms are important in prostate carcinogenesis [19,24]. SAM is required for DNA methylation. Altered DNA methylation and disruption of DNA repair were reported in cancer patients [25], including those with PCA [19]. For example, the glutathione S-transferase 1 can detoxify reactive chemical species through conjugation with reduced glutathione thus preventing or attenuating the development of cancer upon exposure to carcinogens [26]. The lower expression of the π-class glutathione S-transferase 1 was related to hypermethylation of CpG island of the promoter region of π-class glutathione S-transferase 1 in more than 90% of PCA cases [24]. Nakayama et al. observed hypermethylation of the promoter region of the glutathione S-transferase 1 gene in the majority of areas of carcinoma and high grade prostatic intraepithelial neoplasia lesions, but not in the epithelium and hyperplastic epithelium [27]. Therefore, the role of choline in carcinogenesis may be related to the extent of its utilization as a methyl group donor. Since epigenetic mechanisms precede the development of the tumor, follow-up studies can provide information about a potential predictive value for choline levels in cancer.

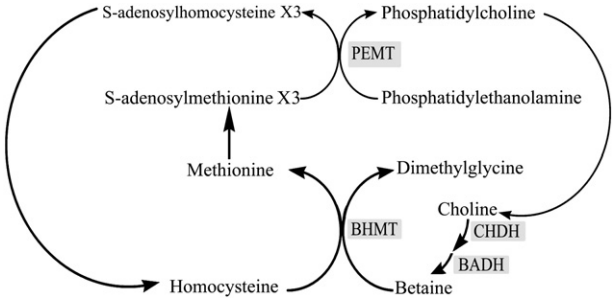

Fig. 1. One-carbon metabolism, the choline cycle. BADH, betaine aldehyde dehydrogenase; BHMT, betaine homocysteine methyltransferase; CHDH, choline dehydrogenase; PEMT, phosphatidylethanolamine *N*-methyltransferase.

The role of choline in phospholipid metabolism

Choline is utilized for the de novo synthesis of PtdCho via the Kennedy pathway (also called CDP-choline pathway) (Fig. 2) [28]. The Kennedy pathway involves three reactions. In the first step, choline kinase (CHK) catalyzes the phosphorylation of choline into PCho. This reaction can be a rate-limiting step for PtdCho biosynthesis [29]. CHK has three isoforms (CHKα1, CHKα2, and CHKβ) all of them have choline kinase activity [30]. The second reaction in the Kennedy pathway is catalyzed by the CTP-phosphocholine cytidylyltransferase (CCT) that yields cytidine diphosphate choline (CDP-Cho) from PCho and cytidine triphosphate (CTP). CCT mediates the rate-limiting step in the Kennedy pathway and its activity depends on the association with membrane structures, the phosphorylation state, and some transcription factors [28,31]. CCTα encodes one isoform and CCTβ encodes three isoforms of the enzyme (β1, β2, and β3). CCTα is found in all tissues, while CCTβ is expressed in certain tissues [32]. In the final step, the CDP-Cho and diacylglycerol (DAG) are converted into PtdCho by 1,2-diacylglycerol cholinephosphotransferase (CPT1). CPT1 seems not to be a rate-limiting step in PtdCho biosynthesis. Choline phosphotransferase and ethanolamine phosphotransferase-1 genes encode the two CPT isoforms, cpt-1 and cept-1, respectively [30,33].

Cancer pathogenesis is discussed in relation to enzymes involved in the synthesis or the degradation of phospholipids. The enzyme CHK seems to enhance the malignant transformation of cancer cells [34]. For example, CHK is overexpressed in PCA thus causing higher PCho and supporting malignant transformation [21]. This in turn enhances choline uptake and membrane phospholipid synthesis in malignant cells [21,35]. Furthermore, PCho might be involved as a second messenger in the growth-signaling cascade [30]. In line with this evidence, the inhibitors of CHK show antitumor activity and reduces tumor growth [30,35].

Moreover, the endogenous synthesis of choline seems to be upregulated in cancer cells. The higher requirements of choline in cancer cells are supported by the enhanced choline transport activities and increased degradation of PtdCho by phospholipase D (PLD). Choline can be synthesized from PtdCho by means of phospholipase A (PLA) and PLD, while phospholipase C (PLC) converts PtdCho into PCho. There are three reactions that produce choline from PtdCho. First, phospholipase A2 (PLA2) catalyzes the hydrolysis of PtdCho yielding 1-acylglycerophosphocholine, which is converted to glycerophosphocholine (GPC) by the enzyme lyso-phospholipase A1 (Lyso-PLA1). The enzyme GPC phosphodiesterase (GPC-PDE) then converts GPC into choline [7]. Recent data demonstrated that GPC-PDE constitutes a source of choline from GPC for the Kennedy pathway [36,37]. Moreover, GPC-PDE has been demonstrated to play a critical regulatory role in cell migration in vitro [37]. Second, choline and phosphatidic acid are produced from PtdCho via two isoforms PLD1 and PLD2 [38]. The activity of the enzyme PLD that synthesized choline from PtdCho is increased in tumor cells [38,39]. Several lines of evidence indicated that PLD might be implicated in cell proliferation, survival signaling,