A potential tumor marker: Chaperonin containing TCP-1 controls the development of malignant tumors (Review)

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Abstract. Due to concealment, high invasiveness and a lack of indicators, malignant tumors have emerged as one of the deadliest diseases worldwide and their incidence is rising yearly. Research has revealed that the chaperonin family member, chaperonin containing TCP-1 (CCT), serves a crucial role in malignant tumors. CCT is involved in the growth of numerous malignant tumors such as lung cancer, breast cancer, hepatocellular carcinoma and colorectal cancer and assists the folding of a number of proteins linked to cancer, such as KRAS, p53 and STAT3. According to clinical data, CCT is highly expressed in a range of tumor cells and is associated with poor patient prognosis. In addition, through controlling the cell cycle or interacting with other proteins (including YAP1, HoXB2 and SMAD2), CCT has an effect on the proliferation, invasion and migration of cancer cells. As a result, it is possible that CCT will become a new tumor marker or therapeutic target, which will provide some guidance for early tumor screening or late tumor prognosis. In the present review, the molecular properties of CCT are introduced, alongside a summary of its interactions with other cancer-related proteins and a discussion of its function in common malignant tumors. It is expected that the present review will offer fresh approaches to the treatment of cancer.

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Contents

1. Introduction

Chaperonins are functional proteins that help newly synthesized polypeptide chains to fold and can be divided into two categories. The first type is GroEL, which is present in fungi, bacteria, mitochondria and chloroplasts. The second type is Chaperonin Containing TCP-1 (CCT or TRiC), which exists in eukaryotic cells (1,2). CCT has the most complex structure of all chaperone proteins and is composed of two cyclic structures, each of which consists of eight adjacent different subunits (CCT1-8) with a molecular weight of ~60 kDa each (3,4). CCT6 is also divided into two subunits, CCT6A and CCT6B (5). Each subunit can be divided into three domains: Apical (substrate binding domain), intermediate (connecting the other two domains) and the equatorial (contains the ATP binding site). The sequences of the equatorial and intermediate domains are conserved, while the sequences of the apical domains are highly differentiated among the eight subunits (6,7). There is a cavity in the middle of the CCT ring that can bind two obligate folding substrates, actin and tubulin (7). The newly synthesized protein folds in this cavity in an ATP-dependent manner (Fig. 1) (1,8). In eukaryotic cells, CCT promotes the folding of ~10% of newly synthesized proteins (1,4), including some cell cycle regulators and tumor-associated proteins, such as cell division cycle protein 20, cadherin 1, STAT3, KRAS and p53 (9-11).

Malignant tumors are one of the diseases with the highest mortality rates due to their concealment and high invasiveness. Therefore, it is important to elucidate more tumor markers. Previous studies have shown that upregulation of

CCT can promote the progression of malignant tumors (12-14). Therefore, exploring genes that can inhibit CCT expression or developing inhibitors against CCT may become the focus of future research. For example, a study found that CCT6A is a target gene of microRNA (miR)-148a/152 (15). The upregulation of miR-148a/152 can inhibit the migration, invasion and proliferation of $CD44^+/CD133^+$ colon cancer stem cells and promote their apoptosis by inhibiting CCT6A expression (15). A clinical study has also demonstrated that treatment with the CCT inhibitor, CT20p, can induce the death of neuroblastoma cells (16).

The purpose of the present review is to introduce the structural characteristics of CCT and its role in the cell cycle and to summarize its mechanism of action in the development of certain cancer types. The present review also aims to provide a new direction for the study of malignant tumors and to provide new targets for early screening and treatment of tumors in the future.

2. Relationship between CCT and the tumor cell cycle

The typical cell cycle for eukaryotes includes four stages: G_1 phase, S phase, G_2 phase and M phase (17). In mammalian cells, growth regulates the cell division cycle mainly by triggering the G_1/S phase transition (18). Excessive cell activity or accelerated S phase entry can lead to tumorigenesis (19). The expression of CCT increases during G_1/S phase transition and when the expression of CCT is decreased, the G_1/S phase transition is delayed, which inhibits cell proliferation, cell viability, cell cycle arrest and apoptosis (Fig. 2) (7,20). In addition, CCT3 serves an important role in regulating the tumor cell cycle and mitosis. Knockout of CCT3 expression can induce apoptosis in lung adenocarcinoma cells, cervical squamous cell carcinoma, endocervical adenocarcinoma cells and breast cancer cells and inhibit tumor cell proliferation, migration and invasion and promoting cell cycle arrest (13,21,22). CCT3 can also significantly inhibit the glycolytic function of cells and reduce the total ATP level in cells by at ≥25% (21). In addition, CCT3 is also a newly discovered spindle integrity regulator as, during mitosis, the connection of centromeres and microtubules require the assistance of CCT3 (23). Therefore, from the current research progress, it is indicated that high expression of CCT can promote the proliferation of cancer cells by regulating the cell cycle. In order to explore its mechanism, it is necessary to study the downstream genes of CCT.

3. Relationship between CCT and tumor-related pathways

CCT and the AKT Pathway. Studies have found that knockout of the CCT gene can inhibit the phosphorylation and activation of AKT and that CCT can interact with AKT and mTOR, activating AKT/mTOR signaling and negatively regulating apoptosis and autophagy (12,24). In particular, CCT3 has been shown to enhance AKT activity in lung adenocarcinoma (LUAD) cells (25). In addition, the AKT inhibitor, MK2206, significantly inhibits the growth of CCT3-overexpressing lung cancer cells (25). In addition, a study has shown that PI3K/AKT signaling pathway-related genes, CCNE1-2, GNB1-5 and TP53, are significantly associated with changes in CCT expression, suggesting that CCT may be used as a therapeutic target for patients with malignant tumors (26). Meng *et al* (27) demonstrated that, knocking down CCT5 can inhibit LUAD cell migration and invasion *in vitro* by inactivating PI3K/AKT and its downstream epithelial-mesenchymal transition (EMT) signals, which could abrogate the accelerated migration and invasion caused by Cyclin D1 overexpression. Guest *et al* (28) used SUM-52 breast cancer cells to demonstrate that fibroblast growth factor receptor 2 signaling regulates CCT expression through PI3K/AKT and that this signaling does not require mTOR activity. In addition, Wang *et al* (25) found that CCT3 promotes LUAD cell growth by inhibiting SLC7A11-mediated iron apoptosis and activating the AKT pathway. In summary, CCT can regulate the proliferation, invasion and migration of cancer cells through the PI3K/AKT/mTOR pathway.

CCT and STAT3. STAT3 is an important oncogenic protein, which can promote the proliferation and survival of cancer cells and control cell cycle progression and apoptosis (29). It has been shown that STAT3 binds to CCT in an ATP-dependent manner through its β-chain-rich DNA binding domain and is a non-specific substrate of CCT (30). The addition of a second TRiC-binding domain (TBD) to the N-terminus of STAT3 (the TBD of pVHL, vTBD) can further increase the affinity of STAT3 for CCT (30,31). STAT3 is present in primary small cell lung cancer (SCLC) tissues and cell lines and is an important target for inhibiting SCLC (32). Carr *et al* (33) found that the CCT inhibitor, CT20p (a polypeptide with cancer-specific cytotoxicity), reduced STAT3 levels in SCLC cell lines and that these cell lines were resistant to cell death induced by STAT3 inhibitors. It has been confirmed that the expression of CCT3 is related to the JAK/STAT3 signaling pathway (34). Danni *et al* (35) found that CCT3 can promote the cisplatin resistance of LUAD cells by activating the JAK2/STAT3 pathway and that CCT3 gene knockout can inhibit the JAK2/STAT3 pathway to re-sensitize A549/DDP cells to cisplatin. This suggests that CCT3 may be a new molecular target for overcoming cisplatin resistance in patients with LUAD. A study (36) showed that CCT3 may play a key role in the transport of phosphorylated (p-)STAT3 and STAT3 from the cytoplasm to the nucleus. CCT3 can enter the nucleus of hepatoma cells with pSTAT3 and the expression of CCT3 is positively correlated with the activation of the STAT3 signaling pathway (36). Since CCT is essential for the synthesis, refolding and activity of STAT3, it has become a potential target for the treatment of cancerous diseases.

CCT and the Wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway serves an important role in embryonic development and the homeostasis of cell proliferation and differentiation in adult tissues. Excessive activation of the Wnt signaling pathway has been found in a number of cancer types, including colorectal cancer (CRC), breast cancer, lung cancer and hematological malignancies (37). In addition, it has been shown that CCT3 target genes are involved in the Wnt signaling pathway (34). Li *et al* (38) found that circular CCT3 RNA directly interacts with miR-613 and regulates the expression of VEGFA and Wnt3 genes. CCT3 deficiency can inhibit the invasion and induce the apoptosis of CRC cells through miR-613/Wnt3 or VEGFA (38). In addition, a study (39) confirmed that, when CCT3 expression is knocked

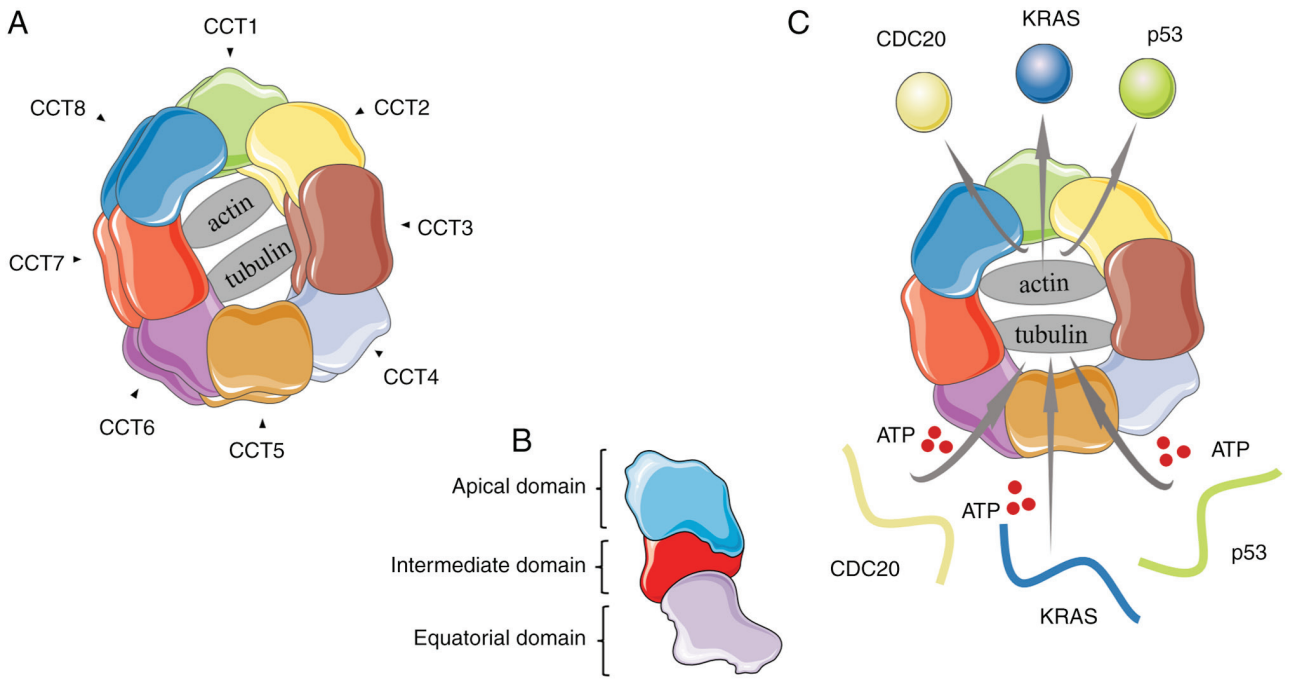

Figure 1. Structure and function of CCT. (A) CCT is composed of two ring structures and each ring consists of eight different subunits. The central cavity of the CCT ring has two substrates: Actin and tubulin. (B) Each subunit of the CCT ring consists of three domains: apical, intermediate and equatorial. (C) CCT3 assists the folding of newly synthesized proteins into correct structures, which depends on ATP. CCT, chaperonin containing TCP-1.

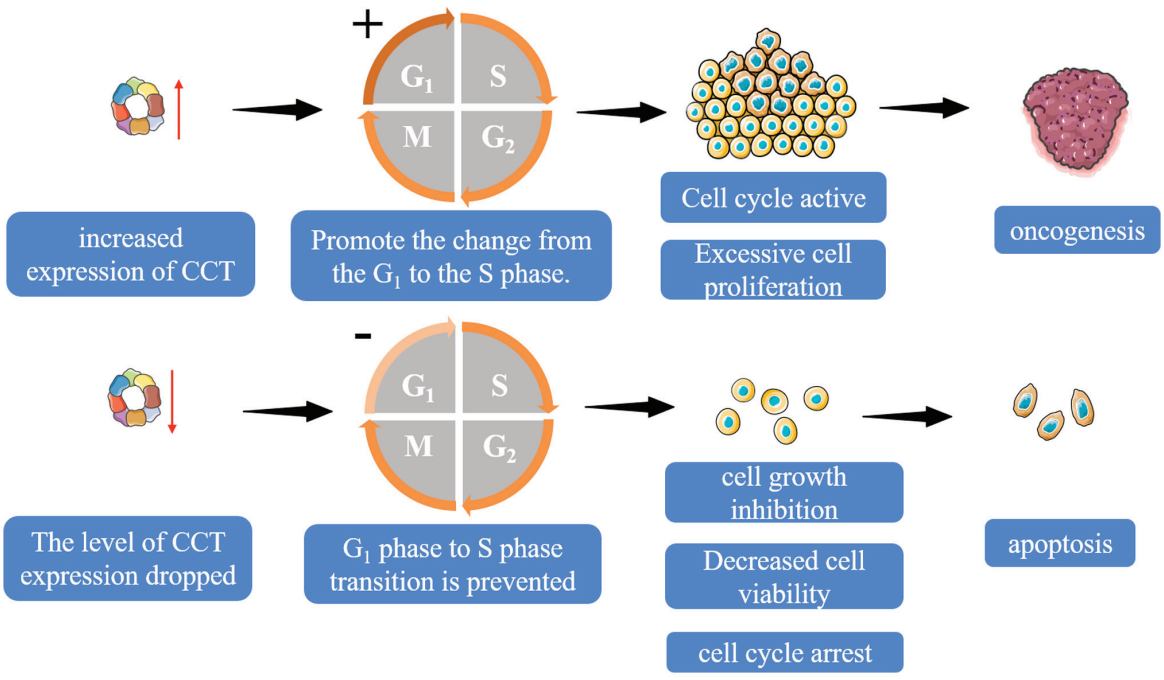

Figure 2. Role of CCT in the cell cycle. CCT affects the development of malignant tumors by controlling the transition of G_1/S phase in the cell cycle. CCT, chaperonin containing TCP-1.

out in breast cancer cells, the expression of Wnt/β-catenin and the downstream target genes, cyclin D1 and c-myc, is inhibited. In addition, when CCT3 expression is upregulated, these genes are also activated accordingly (39). These studies suggest that CCT3 may promote the occurrence of breast cancer by activating the Wnt/β-catenin signaling pathway. Tang *et al* (40) demonstrated that p53 can bind to the second position of the Wnt7b promoter and that CCT interacts with p53 to regulate the Wnt7b/β-catenin pathway. CCT gene knockout can prevent the activation of the Wnt/β-catenin signaling pathway through Wnt7b, thereby inhibiting the proliferation and migration of hepatocellular carcinoma (HCC) cells (40). Therefore, further exploring the relationship between CCT and the Wnt/β-catenin pathway may be a viable direction for studying the mechanism of malignant tumor development (Fig. 3).

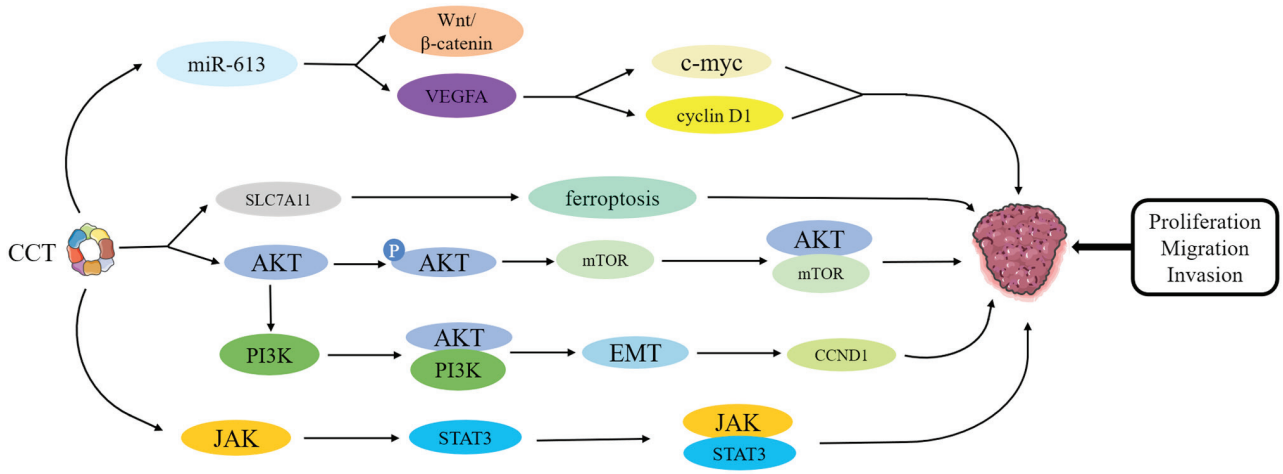

Figure 3. Mechanism of chaperonin containing TCP-1 in regulating the occurrence and development of malignant tumors. miR, microRNA; CCT, chaperonin containing TCP-1.

CCT interacts with p53. p53 is a well-known tumor suppressor protein encoded by the human TP53 (or TRp53) gene and is a major regulator of genomic stability, the cell cycle, DNA repair, senescence and apoptosis (41,42). The point mutation of p53 not only leads to the loss of wild-type activity, but also leads to the occurrence of cancer and the ability of p53 to promote invasion and metastasis (43). A number of studies (6,43,44) have found that the N-terminus of p53 [including its subtype Δ133p53 (45)] binds to seven subunits of CCT to form a CCT-p53 complex to promote p53 folding. When CCT is depleted or the binding is absent, the conformation of p53 is altered, resulting in the accumulation of misfolded p53 and thereby promoting the occurrence and development of tumors (6,43,44). It was found that there was a higher concentration of the more acidic CCT3 variant protein in p53-deficient cells, indicating that CCT3 is a protein rich in potential phosphorylation (46). Ooe *et al* (47) demonstrated that CCT5 was upregulated in breast cancer carrying a p53 mutation, which may be related to docetaxel resistance. Since p53 is one of the most common tumor suppressor genes, it is necessary to further explore the interaction between p53 and CCT.

4. CCT and lung cancer

Overview of lung cancer. Lung cancer is one of the most common malignant tumors and the leading cause of cancer-related mortality (48,49). There is evidence that risk factors for lung cancer often include smoking, age, sex, family history, living environment and occupational exposure (50). It has been demonstrated that 85% of lung cancer cases are related to smoking (51). Histologically, lung cancer can be divided into SCLC and non-small cell lung cancer (NSCLC), accounting for 15 and 85% of all lung cancers, respectively (52). NSCLC can be further divided into LUAD, squamous cell carcinoma, adenosquamous cell carcinoma, large cell carcinoma and sarcomatoid carcinoma (52-55). Current treatments for lung cancer include surgical resection, targeted therapy, immunotherapy, chemotherapy, radiotherapy and adjuvant therapy. Among them, molecular targeting drugs are the main treatment for lung cancer. However, the efficacy of these drugs is often limited and treatment-related toxicity reduces their therapeutic effects. Therefore, there is an urgent need to find new treatment strategies for patients with lung cancer (56-58).

Relationship between CCT and lung cancer. A large number of studies have shown that the subunits of CCT interact with numerous proteins to affect the development of lung cancer cells (59-62). For example, Shi *et al* (59) found that CCT3 silencing inhibited Yes-associated protein 1 (YAP1) and reduced the expression of YAP1 target genes in NSCLC cells. Activation of YAP1 by overexpression of constitutively active YAP1 mutants can reverse the antitumor effect of CCT3 inhibition on NSCLC cells (59). In addition, I-Trp can trigger apoptosis in the highly metastatic CL1-5 NSCLC cell line by interfering with the β-tubulin/CCT2 complex, then activating endoplasmic reticulum stress and finally activating caspases (60). In addition, at the EC_{20} of I-Trp, the migration and invasion of cancer cells were significantly inhibited (60). This strategy can be used to combat highly metastatic LUAD with upregulated CCT2. Ying *et al* (61) identified CCT6A as an inhibitor and direct binding protein of SMAD2 and found that CCT6A promoted metastasis in NSCLC cells. In addition, selective inhibition of SMAD3 or CCT6A can effectively inhibit TGF-β-mediated metastasis (61). This finding may help to develop therapeutic strategies for targeting TGF-β in the treatment of NSCLC. A study (62) confirmed that CCT6A may promote cell proliferation by promoting the transformation of NSCLC cells from G_1 phase to S phase, thereby accelerating tumor growth and determining TNM staging in patients with advanced NSCLC (62). In addition, a study found that CCT6A and CHCHD2 are co-amplified with EGFR in the chromosome 7p11 region and that both are potential driver genes for LUAD (63). The upregulation of CCT6A or CHCHD2 is related to the progression of LUAD (63). In addition, by inhibiting the expression of CCT6A or CHCHD2, the acquired resistance to EGFR tyrosine kinase inhibitors mediated by additional EGFR amplification can be reduced (63).

5. Relationship between CCT and breast cancer

Overview of breast cancer. Breast cancer is the most commonly diagnosed cancer in women worldwide, with nearly 1.7 million confirmed new cases each year, accounting for 25% of all new cancer cases in women (and only 1% in men) (64,65). The number of women diagnosed with breast cancer worldwide is increasing (66). Although the treatment of patients with breast cancer has been greatly improved in recent years, the prognosis of triple negative breast cancer (TNBC) is still relatively poor (67). The lack of drug targets is an obstacle to the treatment of patients with TNBC (68). Since breast cancer is a heterogeneous disease, treatment options and prognosis can vary depending on the hormone receptor status and genetic characteristics of the patient (69). Therefore, it is important to find new tumor markers and targets.

Effect of CCT on breast cancer. The expression of CCT serves an important role in the occurrence and development of breast cancer. Among the CCT subunits, CCT1, CCT3, CCT4, CCT5 and CCT7 had the highest expression levels in TNBC tissues (70). Furthermore, CCT6A and CCT8 were abundant in $HER2^+$ breast cancer tissues and CCT2 was abundant in luminal breast cancer tissues (70). In different histological subtypes of breast cancer, the high expression of CCT6A was negatively correlated with estrogen receptor and progesterone receptor status and positively correlated with nodular, basal and TNBC status (71). CCT expression often activates cell proliferation and abnormal cell proliferation is an indicator of malignant tumor cells (72). Macario *et al* (72) showed that the proliferation index and generation time of cells transfected with CCT2 lentivirus were increased compared with the control cells. Evaluation of cell cycle kinase (such as CDK2 and CDK4) levels found that they were dependent on CCT. Therefore, increased cell proliferation associated with CCT2 upregulation may be related to the kinases that mediate the cell cycle (72). Showalter *et al* (1) observed the division of breast cancer cells and found that the expression of a single CCT2 subunit may induce cell proliferation through the activity of the chaperone protein complex, which increases the levels of key cyclins, such as CDKs. Previous studies have shown that CCT2 is a putative autocrine/paracrine factor and has potential functions in regulating the growth of breast cancer cells (73). Ghozlan *et al* (74) demonstrated that CCT2 is located on chromosome 12q15 and that genetic changes occur in invasive breast cancer and other 12q15 oncogenes. Bassiouni *et al* (75) demonstrated that CT20p mediates its cytotoxicity by inhibiting CCT in breast cancer cells. CT20p can decrease the levels of CCT target proteins, such as actin, tubulin or STAT3, which are necessary for the maintenance, adhesion and survival of cancer cells, leading to cell death (75). For breast cancer cases with high CCT expression, CCT inhibitors may be an effective method for future treatment.

6. Role of CCT in HCC

Overview of liver cancer. The liver is involved in the clearance of human toxins, the uptake of nutrients and the regulation of blood volume and can regulate metabolism and maintain homeostasis (76-78). However, the development of liver tumors often leads to metabolic disorders (76). Furthermore, liver cancer (HCC accounts for 75-85%, cholangiocarcinoma accounts for 10-15%) has become the fourth leading cause of cancer-related mortality worldwide (76,79,80). There are ~840,000 new cases of liver cancer and at least 78,000 individuals succumb to liver cancer each year (81). The global annual incidence rate is ~10.1/100,000 and the morbidity and mortality rates are steadily rising (82-84). Due to the insidious nature of the early stage of liver cancer and the limited accuracy of related markers, treatment is difficult and the prognosis is extremely poor (76,85,86). The median overall survival time of untreated HCC at all stages is estimated to be 9 months (84) and the overall 5-year survival rate is ~20% (34% for local metastasis and 3% for distant metastasis) (86). At present, early liver cancer is mostly treated by surgical resection, but it is prone to complications (87). For advanced liver cancer, several tyrosine kinase inhibitors (such as sorafenib and lenvatinib) and a monoclonal antibody against VEGFR2 (ranibizumab) are used for treatment, but long-term use can lead to drug resistance (87,88). Therefore, it is important to find new liver cancer markers. Tumor biomarkers are of great significance in early screening, diagnosis, treatment evaluation, recurrence and prognosis evaluation of cancer and CCT may provide a new way for early detection and treatment of liver cancer.

Role and clinical significance of CCT in HCC. The expression of CCT in liver cancer cells is closely related to the diagnosis, treatment and prognosis of liver cancer (26,36,89,90). Investigation of selected genes in patients with HCC and validation using The Cancer Genome Atlas database demonstrated that CCT3 was significantly correlated with the overall survival time of patients with HCC (36,90). In addition, the overall survival rate of patients with low expression of cancer cell nuclear CCT3 was higher compared with patients with high CCT3 expression. A study has found that the incidence of CCT gene changes in HCC is as high as 51.39%, which is related to the poor prognosis of patients with HCC (26). When HCC is in the early stage and α-fetoprotein (AFP) is negative, CCT3 can be combined with IQ motif containing GTPase activating protein 3 as a complementary marker of AFP and its expression is independent of AFP (89). A study by Cui *et al* (36) demonstrated that CCT3 accumulates in the cytoplasm and nucleus in HCC cells, while in non-HCC cells, CCT3 mainly accumulates in the cytoplasm. In addition, CCT3 is highly expressed in the nuclei of moderately and poorly differentiated HCC, but expression is lower in the nuclei of highly differentiated and non-HCC (36). Li *et al* (5) found that abnormal expression of the CCT gene was associated with macrophage infiltration and patients with HCC with high CCT gene expression and a high macrophage score had a poor prognosis. This may be due macrophages mainly existing in the immune microenvironment of liver cancer tumors as M2 type (one of the polarization types of macrophages), induced by interleukin-4, is mainly involved in the anti-inflammatory response and tissue repair (91). Huang *et al* (3) demonstrated that, compared with LO2 cells, the expression level of CCT8 in HCC cells was significantly increased and the expression of CCT8 was the most abundant in Huh7 cells. In addition, it was also found that silencing CCT8 inhibited the proliferation of HCC cells by inhibiting the S phase entry of HCC cells (3).

Wong *et al* (92) found that the CCT3 gene expression level in tumors was higher than that in adjacent non-malignant liver tissues in 10 cases of HCC with amplicon 1q21-q22. In addition, Liu *et al* (93) demonstrated that nearly 50% of patients with HCC had CCT gene mutations, of which 27% had CCT3 gene mutations and 18% had CCT5 gene mutations. Furthermore, patients with CCT gene mutations had a worse clinical prognosis compared with patients without mutations.

In terms of mechanism of cell cycle, Zeng *et al* (94) demonstrated that silencing CCT6A could inhibit the expression of cyclin D and block the transition of the cell cycle from G_1 to S phase (the proportion of cells in G_1/S phase increased significantly), thus inhibiting the proliferation of HCC cells. Previous studies have shown that RNA binding protein (RBP) serves an important role in cancer (95-97). A recent study by Sondergaard *et al* (98) found that CCT3 is a new RBP. CCT3 participates in lipid metabolism in liver cancer by forming a CCT3-LINC00326 regulatory network in cells and *in vivo* and reduces fat accumulation in the body, increases intracellular fat degradation and weakens tumor growth (98). Zhang *et al* (99) analyzed the DNA methylation level of identified liver cancer driver genes and found that CCT3 had high expression and low methylation, indicating that it can participate in the occurrence of HCC by regulating methylation status. Xu *et al* (100) found that miR-139-5p inhibited HCC tumor invasion and was negatively correlated with CCT5. The miR-139-5p/CCT5 axis may play an important role in the development of HCC.

7. Relationship between CCT and CRC

Overview of CRC. CRC is the third most common cancer worldwide and the second leading cause of cancer-related mortality (101,102). CRC is a multifactorial disease involving genetic, environmental and lifestyle risk factors (103). The high heritability and frequent recurrence of CRC leads to considerable mortality and the association with poor prognosis (104). At 2020, there were >1.9 million new cases of CRC (including anal) and nearly 935,000 mortalities in worldwide (105). CRC accounts for 9.2% of global deaths, with 5- and 10-year survival rates of 65 and 58%, respectively (106). The incidence and mortality rates are 25% higher in men than in women (106). Although the treatment strategy of CRC has been greatly improved, including colon resection, chemotherapy and immunotherapy, the high frequency of recurrence and metastasis makes CRC a serious threat to human health (107,108). The 5-year survival rate of patients diagnosed with advanced CRC, especially those with distant metastasis, remains low, at ~13% (109,110). Therefore, it is necessary to find new biomarkers for early diagnosis, accurate prediction of metastasis and prognosis.

Role of CCT in CRC. Zhu *et al* (111) found that CCT1 was highly expressed in 87.9% of colon cancer tissues and positively correlated with tumor invasion and tumor size. In addition, Coghlin *et al* (112) demonstrated that CCT2 and CCT5 were upregulated in colorectal adenocarcinoma. A cell localization study indicated that CCT2 was localized to the cytoplasm, while CCT5 staining was visible in the nucleus and cytoplasm in CRC (112). In addition, the expression of CCT2 and CCT5 increased with the progression of Dukes stage and upregulation of cytoplasmic CCT2 is also associated with reduced survival time in patients (112). Yokota *et al* (113) found that the levels of CCT1 and CCT2 in the cytoplasm of HCC and colon cancer cells are often upregulated and effectively produce the proteins needed for growth. Since CCT is widely distributed in the cytoplasm, it may be a useful tumor marker.

Yang *et al* (114) found that overexpression of the transcription regulator, HoXB2, could block the inhibitory effect of CCT6A gene knockout on the proliferation, migration and invasion of colon cancer cells and that HoXB2 increased the proliferation and invasion of colon cancer cells by upregulating the expression of CCT6A. Liu *et al* (115) demonstrated that I-Trp can destroy the CCT2-β-tublin complex in tumor cells and selectively kill cells compared with normal cells. In addition, CCT2 gene knockout can decrease the cytotoxicity of I-Trp (115). Park *et al* (116) found that the CCT2-Gli-1 interaction can be induced under hypoxia to enhance the folding of Gli-1. Therefore, downregulation of CCT2 may decrease the stability of Gli-1 and inhibit the tumorigenicity of Gli-1 (116). Sun *et al* (117) found that CCT6A was upregulated in colon adenocarcinoma (COAD) and that CCT6A is associated with poor prognosis and reduced immune infiltration (such as $CD4^+$ T cells, B cells and dendritic cells). Hu *et al* (118) identified CCT6A as a biomarker of pre-depleted T cell subsets in CRC by dynamic network biomarker (DNB). In addition, TUBA1B gene expression is triggered by CCT6A as DNB core gene contributes to the depletion of $CD8^+$ T cells, indicating that the core gene acts as a biomarker in pre-depleted T cells (118). Using mouse experiments, Lu *et al* (119) demonstrated that CCT is a drug carrier that binds to TNF-α, promotes the absorption of 5-fluorouracil (5-FU) in tumors and inhibits the development of colorectal tumors. In combination therapy, CCT/TNF-α + 5-FU had a more significant antitumor effect than TNF-α + 5-FU (119,120). Liao *et al* (121) found that CCT8 can antagonize wild-type p53 cell cycle arrest and EMT transcriptional inhibition by inhibiting wild-type p53 into the cell nucleus, thereby promoting the proliferation, invasion and metastasis of CRC.

8. Conclusion

Cancer cells frequently have an unbalanced cell cycle. Accumulating data indicates a crucial role for CCT in the control of cell cycle progression. The development, proliferation and death of eukaryotic cells are all influenced by CCT, which is crucial for the folding of newly generated proteins. The expression of CCT is significantly increased during cell division, which aids in the folding of actin and other tumor-associated proteins necessary for cell division. Finding new biomarkers is crucial to advancing early detection and treatment of cancer, which is especially critical given the rising incidence of the disease. CCT is significant in a number of illnesses. Maintaining living cells requires both the folding of newly generated proteins and the preservation of proteins. Proteolytic turnover, intracellular localization and protein folding are all closely regulated by the molecular chaperone network. Therefore, CCT is a potential diagnostic for malignant tumors since numerous important regulators of cell growth and differentiation have been identified as target proteins for molecular chaperones.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

LZheng and XC drafted the manuscript and contributed equally. LZhang and NQ participated in the literature search and analysis of the data to be included in the review. JA and JZ were involved in the design of the study and assisted in the preparation of the figures and tables. HJ and BT edited and revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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