Protein Kinase CK2, a Potential Therapeutic Target in Carcinoma Management

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Abstract

The Protein kinase CK2 (formerly known as casein kinase 2) is a highly conserved serine/threonine kinase overexpressed in various human carcinomas and its high expression often correlates with poor prognosis. CK2 protein is localized in the nucleus of many tumor cells and correlates with clinical features in many cases. Increased expression of CK2 in mice results in the development of various types of carcinomas (both solids and blood related tumors, such as breast carcinoma, lymphoma, etc), which reveals its carcinogenic properties. CK2 plays essential roles in many key biological processes related to carcinoma, including cell apoptosis, DNA damage responses and cell cycle regulation. CK2 has become a potential anti-carcinoma target. Various CK2 inhibitors have been developed with anti-neoplastic properties against a variety of carcinomas. Some CK2 inhibitors have showed good results in in vitro and pre-clinical models, and have even entered in clinical trials. This article will review effects of CK2 and its inhibitors on common carcinomas in in vitro and pre-clinical studies.

Keywords: Protein kinase CK2- solid tumors- hematological tumors- CX-4945- CIBG-300

Introduction

Protein kinase CK2 is a highly conserved serine/threonine kinase that is ubiquitously expressed in a variety of eukaryotic cells. CK2 kinase may act as a monomeric kinase alone or as a tetrameric complex, which consist of 2 catalytic subunits (CK2α and/or CK2α’) and 2 regulatory subunits CK2β. Its catalytic part is encoded by two genes, CK2α (CSNK2A1) and CK2α’ (CSNK2A2). In mouse tissues, expression levels of CK2α are higher than those of CK2α’ (Xu et al., 1999b). A separate gene CSNK2B encodes the regulatory subunit CK2β, which regulates the substrate specificity of CK2 kinase and enhances the catalytic subunit stability in the tetrameric complex of CK2 (Bibby et al., 2005). In addition, an intron less CK2α pseudo-gene (CK2αP) can be activated in mammalian cells and is, to some extent, associated with carcinomas (Wirkner et al., 1992; Ortega et al., 2014). Interestingly, CK2 subunits mutually regulate their protein expression levels. For example, inhibition of CK2α can reduce CK2β expression or vice versa (Zhang et al., 2002; Olsen et al., 2010).

Protein kinases are the largest family among kinases. Protein kinases act on specific substrates and phosphorylate them to alter their activity. Protein kinase CK2 claims a diverse range of substrates. Researchers described that the number of CK2 substrates was 307 in 2003 (Meggio et al., 2003) and the number has increased greatly afterward. About one third of CK2 substrates are involved in gene expression and protein synthesis, including transcription factors, DNA / RNA structural and translational elements. Many substrates are involved in signal pathways, the source of viruses, or crucial to the life cycle of viruses. A small number of CK2 substrates are classical metabolic enzymes. It is assumed that the CK2 monomeric enzyme is more conducive to the production of phospho-protein in eukaryotic cells than any other protein kinase. CK2 is widespread in eukaryotes and involved in almost all kind of key processes in the cells. It enhances cell proliferation (Pinna et al., 1997; Ahmed et al., 2000), cell growth (Litchfield, 2003), cell survival (Ahmed et al., 2002; Ahmad et al., 2008), changes cell morphology (Canton et al., 2006), increases cellular transformation (Seldin et al., 2005; Domínguez et al., 2009) and promotes angiogenesis (Kramerov et al., 2008; Montenarh, 2014). Thus CK2 plays a very important role in the growth and development of vertebrates.

There are two kinds of CK2α genes in zebra fish (CK2α and CK2α’) and one kind of CK2β gene (Daniotti et al., 1994; Antonelli et al., 1996). The expression levels of CK2α gene after 1 hour post fertilization (hpf) were higher than those after 24 hpf. There was no difference in the transcription levels of CK2β between 1 and 24 hpf. The formation of zebra fish gastrula (5-10

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hpf), three-germ layered embryo, requires CK2. DMAT, a specific inhibitor of CK2, delays the gastrulation in zebrafish embryos (Finkielstein et al., 2009). CK2 may inhibit the activity of PTEN by phosphorylation during gastrulation, thus impairs cell motility associated with gastrulation (Finkielstein and Kelly, 2009). In addition, CK2 also affects angiogenesis in zebrafish embryos. Emodin inhibits CK2 and suppresses the proliferation and migration of endothelial cells, the formation of endothelial cell tube and vascularization (Crawford et al., 2011).

1. CK2 and embryo development

In mouse embryos, the activity of CK2 peaks at 12 days of pregnancy days 12(E12) and decreases at birth (Schneider et al., 1986). Mouse, mRNA and protein of CK2a and CK2b have different temporal and spatial expression patterns in different organs from day E10.5 to E18.5 (Mestres et al., 1994). CK2α and CK2β are enriched in neuroepithelial and epithelial cells, with high levels in epithelial cells at E10.5 and neuroepithelial cells at E11.5 (Mestres et al., 1994). CK2 is also expressed in heart, skeletal muscle, connective tissues and cartilage (Mestres et al., 1994; Lou et al., 2008). The deletion of CK2α results in the death of mice at E11 while loss of CK2β results in early death of mice at E6.5 (Buchou et al., 2003). Mice can survive without CK2α, but male mice become infertile (Xu et al., 1999a).

2. CK2 and tumor

The expression of CK2 is often found aberrant in carcinoma cells. Research data have shown that overexpression of CK2 in mice induces carcinoma, suggesting CK2 plays an important role in the carcinoma pathogenesis (Domínguez et al., 2005; Seldin et al., 2005; Domínguez et al., 2009; Ruzzene et al., 2010; Zhang et al., 2015). The ability of protein kinase CK2 to promote tumorigenesis, to a large extent, depends upon, how it modulates key signaling pathways, which may be different among various carcinomas. CK2 regulates a number of signaling cascades such as Wnt (Domínguez et al., 2004; Domínguez et al., 2005), Hedgehog (Jia et al., 2010), NF-kB (Domínguez et al., 2009), JAK / STAT (Zheng et al., 2011), and PTEN / P13K / Akt-PKB (Torres et al., 2001; Miller et al., 2002; Di Maira et al., 2005; Park et al., 2013) signaling pathways. Dysregulation of these signaling pathways can lead to tumorigenesis. CK2 promotes tumorigenesis in a variety of ways, such as enhancing the stability of MYC proto-oncogene (Channavajhala et al., 2002), activation of NF-kB (anti-apoptotic factor) (Romieu-Mourez et al., 2002), inhibition of DNA repair and inhibition of the tumor suppressor phosphatase, PTEN (Torres and Pulido, 2001; Miller et al., 2002).

Various CK2 chemical inhibitors with good cell permeability have been developed. The most commonly studied inhibitors are CX-4945 (Siddiqui-Jain et al., 2010), CIGB-300 (Perea et al., 2008), TBB (Sarno et al., 2001), DMAT (Pagano et al., 2004), Quinalizarin (Cozza et al., 2009), hematin (Hung et al., 2009), TBCA (Pagano et al., 2007), DRB (Zandomeni et al., 1986), apigenin (Hagiwara et al., 1988), Emodin (Yim et al., 1999) and TF (Gotz et al., 2012). Among them, CX-4945 and CIGB-300 have been entered in clinical trials to test their anti-tumor effects and toxic side effects in human.

2.1 The expression and role of CK2 in solid tumors

Expression of CK2 mRNA and protein is variable in different tumors. mRNA and protein levels of CK2 are up-regulated in many carcinomas. In some cases, an increase in CK2 protein levels was detected with no changes in mRNA levels (Tawfic et al., 2001). We have noticed that not all published data support the notion that overexpression of CK2 is driver for tumorigenesis and associated with poor prognosis. CK2 gene expression is down-regulated in some tumors (e.g, CK2α is down-regulated in breast, ovarian and pancreatic carcinomas) and up-regulation of CK2 gene in some tumors correlates with increased survival time (e.g, adenocarcinoma of lungs) (Wirkner et al., 1992; Ortega et al., 2014). Nonetheless in general, up-regulation of CK2 mRNA and / or protein is associated with poor prognosis.

The overexpression of CK2 is associated with poor prognosis of many common solid tumors, including those associated with the chronic exposure to carcinogen such as head and neck carcinomas, non-small cell lung carcinoma, urinary bladder carcinoma or mesothelioma. CK2 is also involved in the pathogenesis of gastrointestinal malignancies, including hepatobiliary carcinoma, esophageal carcinoma and gastric carcinoma, and other types of tumors such as renal carcinoma, cervical carcinoma and glioblastoma multiforme. Table 1 summarizes expression levels of CK2 in common malignant solid tumors and its effects on tumor biological behavior. When there is no publicly published data, expression levels of CK2 are unlabeled in that type of tumors.

2.1.1 The role of CK2 inhibitors in solid tumors

Based on the abnormal expression of CK2 in most of malignant solid tumors, it seems possible to treat those tumors with a CK2 inhibitor. In most malignancies, it has been demonstrated that inhibition of CK2 can affect the biological behavior of tumor cells in both in vivo and in vitro experiments. CK2 inhibitors reduce the migration and invasion of human adenocarcinoma and non-small cell lung carcinoma (NSCLC) cells by down-regulating the transcriptional expression and activity of MMP-2 via the ERK pathway (Ku et al., 2013). The use of CK2 inhibitors (e.g TBCA, TBB and hematin) along with radiotherapy significantly reduced the number of cells in four different types of large cell lung carcinoma (LCLC) and adenocarcinoma cells compared with single drug therapy or radiotherapy alone (Lin et al., 2011). Quinazolin inhibits the viability of adenocarcinoma cells with EGFR mutations more significantly than those without EGFR mutations (Zhou et al., 2015). The inhibitor hematin reduced lung adenocarcinoma cell colony formation, phosphorylated AKT levels, and increased PARP fragmentation (Hung et al., 2010). In xenograft models of lung adenocarcinoma, Hematin was also found suppressing tumor growth (Hung et al., 2013).
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containing RNAi-CK2α/α’) significantly reduced tumor volume, decreased the number of metastases and increased the survival time of mice (Unger et al., 2014). In addition, tumors of mice treated with CK2α/α'-RNAi showed reduced staining of proliferating proteins (such as cyclin D1) and up-regulation of tumor suppressor genes (such as P53) compared with tumors of control mice (Brown et al., 2010).

Glioblastoma multiforme

Preclinical xeno-grafted glioblastoma multiforme (GBM) models demonstrated that various CK2 inhibitors were effective in inhibiting tumors growth and enhancing survival in mice (Prudent et al., 2010; Moucadel et al., 2011; Zheng et al., 2013; Nitta et al., 2015; Chou et al., 2012).

Table 1. CK2 Expression Level in Common Malignant Solid Tumors and Its Influence on Biological Behavior of Carcinoma

| Tumor Type                      | Expression Level of CK2 | Affected Biological Behavior                                                                 |
|---------------------------------|-------------------------|---------------------------------------------------------------------------------------------|
| Lung carcinoma                  | CK2α, CK2α’, CK2β, CK2αP↑* | Cell proliferation, survival, migration and invasion, maintenance of stem cell                |
| Mammary carcinoma               | CK2α↑, CK2β↑, CK2α’↓*    | Cell morphology, proliferation (anchorage-independent proliferation), migration and invasion  |
| Urothelial carcinoma            | CK2α↑                    | Cell cycle arrest, metastasis                                                                |
| Head and neck carcinoma         | CK2α, CK2α’ and CK2β↑    | Cell cycle regulation, proliferation, metastasis, tumor stem cell-like cell maintenance      |
| Mesothelioma                    | CK2α↑                    | Cell Proliferation                                                                          |
| Hepatocellular carcinoma        | CK2α, CK2α’↑             | Cell proliferation and colony formation, cell cycle distribution, apoptosis, migration and invasion |
| Gastric carcinoma               | CK2α↑                    | Cell proliferation, migration and apoptosis                                                  |
| Esophageal carcinoma            | CK2α↑                    | Invasiveness, cell proliferation and metastasis                                              |
| Cholangiocarcinoma              | CK2β↑, CK2α↑             |                                                                                             |
| Colorectal carcinoma            | CK2α↑                    | Cell proliferation, cell cycle distribution, cell motility and invasiveness                  |
| Pancreatic carcinoma            | CK2α’↑                   | Apoptosis                                                                                   |
| Cervical carcinoma              | Not yet clear             | Cell proliferation, tumor stem cell maintenance                                             |
| Glioblastoma                    | CK2α, CK2α’↑             | Proliferation, apoptosis, cell cycle, adhesion, migration and molony formation, autophagy, stem cell phenotype maintenance |
| Melanoma                        | CK2α↑                    | Cell proliferation                                                                          |
| Ovarian carcinoma               | CK2α↑                    | Tumor stem cell maintenance                                                                  |
| Prostatic carcinoma             | CK2α↑                    | Apoptosis, invasion                                                                         |
| Renal cell carcinoma            | CK2α, CK2α’ and CK2β↑    | Cell survival                                                                               |

*Head and neck tumors*

In head and neck squamous cell carcinoma (HNSCC), antisense CK2α decreased the number of cells (Faust et al., 2000; Brown et al., 2010) and induced apoptosis (Wang et al., 2001; Brown et al., 2010). Similarly, antisense CK2β also induced apoptosis (Faust et al., 2000; Brown et al., 2010). Knock-down of CK2α, CK2α’ or CK2β alone left the HNSCC cell arrested in the G0 / G1 phase. Similarly, CX-4945 reduced the number of HNSCC cells, induced cell cycle arrested in S or G2 / M phases, and increased apoptosis (Bian et al., 2015). CK2 inhibitors have reduced tumor load in preclinical models of head and neck carcinomas. In HNSCC xenograft tumor models (lingual carcinoma, hypopharyngeal and laryngeal carcinoma), CK2 inhibitor (nano-capsules containing RNAi-CK2α/α’) significantly reduced tumor volume, decreased the number of metastases and increased the survival time of mice (Unger et al., 2014). In addition, tumors of mice treated with CK2α/α’-RNAi showed reduced staining of proliferating proteins (such as cyclin D1) and up-regulation of tumor suppressor genes (such as P53) compared with tumors of control mice (Brown et al., 2010).

*Glioblastoma multiforme*

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Inhibitors also decreased the activation of AKT, c-MYC, STAT-3, NF-κB, and the expression of EGFR, indicating that CK2 regulates various signaling pathways responsible for proliferation and survival (Zheng et al., 2013; Chou et al., 2016). In addition, silencing of CK2 alone or with EGFR increased tumor necrosis and mouse survival rate (Chou et al., 2016). Therefore, for patients with GBM who have undergone surgical resection plus radiotherapy combined with temozolomide adjuvant chemotherapy, the use of CK2 inhibitors may, to a certain extent, prevent tumor recurrence.

Hepatocellular carcinoma

In hepatocellular carcinoma (HCC), DMAT and CK2α shRNAs inhibited the growth of tumors in a mouse xenograft model of liver carcinoma (Sass et al., 2011; Zhang et al., 2015). DMAT acts by reducing tumor cell proliferation with no effects on cell survival nor angiogenesis, and more importantly with no liver damage, through a mechanism that is mediated by the reduction of NF-κB and activation of Wnt/β-catenin signaling pathways (Sass et al., 2011). In addition, CK2 inhibitors also potentiated the efficacy of chemotherapeutic agents (5-fluorouracil, doxorubicin, or sorafenib) and helped in preventing the spread of HCC (Kim et al., 2008; Sass et al., 2011). These results indicated that CK2 inhibitors can effectively treat liver carcinomas as single or along with other remedies.

Pancreatic carcinoma

In mouse xeno-grafted pancreatic carcinoma models CX-4945 inhibited the tumor growth and reduced p21 staining (Siddiqui-Jain et al., 2010). In addition, intra-peritoneal injection of O-methyl-modified CK2α siRNA resulted in a significant decrease in tumor volume and increased apoptosis of pancreatic carcinoma in mice (Giroux et al., 2009). The use of CK2α siRNA in combination with PAK7 and/or MAP3K7 siRNA significantly reduced tumor volume (Giroux et al., 2009). Above treatments did not affect the body weight of mice. These data suggested that CK2 inhibitors can be used as an effective treatment for pancreatic carcinoma.

Cervical carcinoma

Apigenin inhibition the formation and self-renewal of sphere-forming cells (SFCs) of HeLa cells in cervical carcinomas, whereas overexpression of CK2α conversely increased their capacity of self-renewal (Liu et al., 2015). CK2 inhibitor, CIGB-300 also inhibited cervical carcinoma cell proliferation and tumor growth in a mouse xeno-graft model even after treatment cessation (Siddiqui-Jain et al., 2010; Perera et al., 2014). Further, CIGB-300 had a synergistic effect with paclitaxel and doxorubicin and had an additive effect with cisplatin (CDDP). In combination with cisplatin, it could significantly slow the tumor growth and increase the survival of mouse (Perera et al., 2014).

CIGB-300 has also entered clinical trials to verify its anti-tumor effects on cervical carcinoma. In this clinical trial, 31 female patients with cervical carcinoma underwent CIGB-300 treatment. Drug was administered sequentially with increasing dosage for consecutive 5 days. Adverse effects were minimum even with the highest dose, and tumors were significantly reduced in 75% of the patients. Strikingly, 19% of patients had complete recovery (histologically proven) and 48% of patients became negative for HPV DNA at the end of the trial (Solares et al., 2009). After one year follow-up, there was no recurrence and no adverse event observed. Moreover, among treated patients, four were pregnant and two of whom were infertile before the intervention (Solares et al., 2009). Pharmacokinetic studies have provided the basis for CIGB-300’s treatment in Phase II clinical trials (Sarduy et al., 2015). Therefore, human body can tolerate the inhibition of CK2. CK2 inhibition alone or with other chemotherapeutic drugs are promising for the treatment of cervical carcinoma (Liu et al., 2015). Another open clinical trial is currently undergoing in Argentina. Researchers use CIGB-300 for treating squamous cell carcinoma on, IIA and IIB FIGO stage patients with cervical adenocarcinoma, combined with external radiotherapy, intracavitary brachytherapy and weekly systemic treatment with cisplatin (trial number: NCT01639625).

Ovarian carcinoma

CX-4945, cisplatin and gemcitabine synergistically increased the apoptosis of A2780 tumors cell (Ovarian carcinoma cell line) with wild-type p53 while there was no change in the apoptosis of p53 null SKOV-3 cells (Siddiqui-Jain et al., 2012). The combination of CX-4945 with dasatinib (tyrosine kinase inhibitor) promoted apoptosis in an epithelial ovarian carcinoma cells (Pathak et al., 2015). In a xeno-grafted model (A2780 cells), the survival time of mice treated with CX-4945 along with 3 other drugs (cisplatin, carboplatin, and gemcitabine) was double to that of untreated control. Interestingly, carboplatin has a synergistic effect with CX-4945, whereas cisplatin and gemcitabine have additive effects on the inhibition of tumor growth. Therefore, CK2 inhibitors can be used to treat advanced ovarian carcinomas.

Prostate carcinoma

Proliferation of prostate carcinoma cells can be reduced by CK2 inhibitors (TF, TBB, DMAT, TBCA siRNA, apigenin, and K1-CK2α) (Wang et al., 2005; Schneider et al., 2009; Gotz et al., 2012; Trembley et al., 2012; Yao et al., 2012; Trembley et al., 2014), while the apoptosis was increased (Wang et al., 2008; Schneider et al., 2009; Hessenauer et al., 2011; Pierre et al., 2011; Gotz et al., 2012; Yao et al., 2012; Qaiser et al., 2014). CX-4945, TBCA and apigenin induced cell cycle arrested at the G2/M phase (Pierre et al., 2011; Yao et al., 2012). Furthermore, DMAT and CK2α/a’ siRNAs were capsulated and were found to specifically reduce the proliferation of the prostate carcinoma cell line (PC3-LN4) but not the benign cell line (BPH-1) (Trembley et al., 2012). CK2α/a’ siRNAs also affected C4-2 prostate carcinoma cell line but not normal prostatic epithelial cell line (Funfschilling et al.; Trembley et al., 2012). The inhibition of CK2 can reduce tumor load in xeno-grafted mouse models. CK2α/a’ siRNA, RNAi (Ahmed et al., 2016) and CX-4945 (Pierre et al., 2011)
reduced tumor volume in metastatic PC-3-derived xeno-grafted models. DMAT decreases the proliferation of PC3-LN4 cell-derived xeno-grafted tumors and decreased protein levels of CK2α and CK2α‘ (Trembley et al., 2014).

Breast carcinoma
In preclinical studies of breast carcinoma, CX-4945 reduced the growth of tumors in a mouse model of orthotopic xeno-transplantation of breast carcinoma with no body weight loss and no significant toxicity (Siddiqui-Jain et al., 2010). Inhibition of CK2 can also enhance the sensitivity of breast carcinoma to antitumor drugs. DMAT effectively reduced the number of cells, increased apoptosis and altered cell morphology in breast carcinoma cells resistant to tamoxifen (Yde et al., 2007). CK2 inhibitors are potential therapeutic agents for triple-negative and estrogen-tolerant breast carcinoma.

2.1.2 The combination of CK2 inhibitors and other antitumor drugs
CK2 plays a role in tumor chemotherapeutic drug resistance. CK2 has been considered to mediate resistance to cisplatin in gastric carcinoma cell, as increased levels of CK2α protein have been observed in these types of carcinomas (Xu et al., 2014). In addition, CK2 protected colon carcinoma cells from TRAIL (TNF related apoptosis inducing ligand) induced apoptosis. Reciprocally inhibition of CK2 phosphorylation by DRB resulted in increased cells apoptosis induced by TRAIL in colon carcinoma cells. shRNA interference with CK2α also increased the sensitivity of human colorectal adenocarcinoma cells to TRAIL (Izeradjene et al., 2005).

Perera et al., (2014) have observed the synergistic interaction between CK2 inhibitor CIGB-300 and other chemotherapeutic drugs, in the preclinical tumor models of lung carcinoma and cervical carcinoma (Liu et al., 2015). They used Cisplatin (alkylation), 5- fluorouracil (DNA/RNA antitumorabolite), Paclitaxel (anti-mitosis), and Doxorubicin (anti topoisomerase II) to treat lung carcinoma and cervical carcinoma cells. Results showed excellent synergistic / additive effects of cisplatin and paclitaxel with CIGB-300, according to the combination and dose reduction index. Paclitaxel showed the strongest synergistic effect in combination with CIGB-300 in SiHa and NCI-H125 cell lines and exhibited the same inhibitory effect on cell proliferation with reduced dose (1/5 of normal CIGB-300 dosage). These findings provided a theoretical basis for the clinical combination of anti-CK2 (CIGB-300) and other antitumor drugs, and suggested that platinum and taxane can be used as anti-cancer drugs with good prospect. Similarly, CX-4945 has been studied in combination with erlotinib (an EGFR tyrosine kinase inhibitor) for the treatment of advanced non-small cell lung carcinoma. Bliesath et al., (2012) investigated the combined effect of CX-4945 and erlotinib in non-small cell lung carcinoma and squamous cell carcinoma in both, \textit{in vitro} and \textit{in vivo}. They found significant inhibition of the PI3K-Akt-mTOR signaling pathway and tumor growth arrest with the combination treatment. Additionally, they noticed the decreased cell proliferation and increased cell apoptosis after combination treatment. In conclusion, these data suggested that CK2 can be used as an effective pharmacological target for combination treatment of carcinomas. Studies also emphasized on further exploration of combined effects of CX-4945 and EGFR targeting agents (Bliesath et al., 2012).

The combined use of CX-4945 with gemcitabine and cisplatin in the treatment of cholangiocarcinoma is currently undergoing phase I / II clinical trial. CX-4945 can inhibit DNA repair and is particularly effective in combination with DNA damaging drugs such as cisplatin. The purpose of this clinical study is to determine the maximum-tolerated dose (MTD) of drugs and compare the antitumor activity of standard gemcitabine / cisplatin with that of the combination of three drugs. This project has been conducted at a number of central research institutes in the United States, South Korea and Taiwan. The completion date of the study was December 2017 (test number: NCT02108282). No report has been published yet.

2.2 CK2 and Hematological tumor
Hematological tumors are mostly liquid tumors. Their cells exist in blood circulation, and can invade any hematopoietic organ and tissue. The treatments of lymphoma and myeloma have been greatly improved. CK2 inhibitors may be of little use in some cases. But there are still other reasons for their usage, especially in cases of acute leukemia.

2.2.1 Non-Hodgkin’s lymphoma (NHL)
Recently multiple drugs are available for the treatment of NHL, but there is still a strong need for new treatment with better efficacy and less adverse effects. A recently published study showed that levels of CK2α and CK2β protein increased in Burkitt’s lymphoma, DLBCL, follicular lymphoma, and lymphoma cell lines (Pizzi et al., 2015). CK2 inhibitor CX-4945 can induce a dose-dependent increased apoptosis in Burkitt’s lymphoma and DLBCL cells (Pizzi et al., 2015), while CX-4945 does not affect normal peripheral blood mononuclear cells. In animal models, the increased expression of CK2α in lymphocytes of transgenic mice led to the occurrence of T cell lymphoma (Seldin, 1995; Seldin et al., 1995; Channavajhala and Seldin, 2002). These data suggested that the development of CK2 inhibitors is still of great significance for the treatment of NHL.

2.2.2 Multiple myeloma
Although treatment options for multiple myeloma (MM) have increased rapidly in recent years, but in most cases the final results are deterioration or death. Therefore, there is still a need to explore new treatment options for better management. CK2 kinase activity and CK2α protein levels increase in bone marrow cells of multiple myeloma patients (Piazza et al., 2006; Manni et al., 2013). Similarly, CK2α and CK2β staining increased significantly in multiple myeloma tissue samples (Manni et al., 2013). Inhibition of CK2 by IQA, TBB, apigenin and TBB derivative K27 (2- amino -4,5,6,7- four bromo -1H- benzimidazole) (Zhao et al., 2011) can reduce the viability and increase the apoptosis of myeloma cells.
This suggested that CK2α plays a role in the survival of myeloma cells (Piazza et al., 2006; Manni et al., 2013; Piazza et al., 2013).

CK2 inhibitors induced the impairment of NF-κB-dependent transcriptional activity (Piazza et al., 2006) and also downregulated endoplasmic reticulum (ER) stress response, resulted in increased apoptosis (Manni et al., 2013). This is because myeloma cells produced abnormally excessive quantity of antibodies. ER-stress/unfolded protein response is essential for the survival of myeloma cells. Existing studies have shown that CK2 inhibitors act synergistically with the conventional chemotherapeutic drug, Melphalan, to increase cytotoxicity (Piazza et al., 2006). CK2 inhibitors combined with geldanamycin (an anti-cancer drug) also have a cumulative effect and can increase the apoptosis of cells (Manni et al., 2013). Therefore, CK2 inhibitors can enhance the sensitivity of myeloma to chemotherapy and reduce its required dosage (Piazza et al., 2006). All above mentioned studies indicated that CK2 might represent a potential target in MM therapy.

### 2.2.3 Leukemia

CK2 plays an important role in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The activity of CK2 and its protein levels are up-regulated in primary B-ALL, T-ALL, AML, and CLL cells (Martins et al., 2010; Gomes et al., 2014; Song et al., 2015). In AML patients, high CK2α protein levels are the predictor of the overall survival rate (Kim et al., 2007). CK2 participates in multiple blood tumor related signal transduction pathways, including PI3K/AKT/PTEN, JAK/STAT, NF-κB and others (Piazza et al., 2012). PI3K/AKT/PTEN cascade regulation is crucial for survival and proliferation of ALL, CLL, and AML tumor cells. In chronic myeloid disease (CMD) and multiple myeloma (MM), CK2 regulates the activation of JAK / STAT, downstream of cytokine / growth factor signaling. CK2 mediates IκBα phosphorylation (Located in the PEST domain) and causes the latter to be degraded by the proteasomal pathway. After the degradation of IκBα, NF-κB p65 enters into the nucleus, where CK2 mediates Ser529 phosphorylation of NF-κB p65 to activate NF-κB pathway. This pathway is very important for the survival of CLL and MM cells as it provides the resistance to chemotherapeutic drugs.

In AML cell lines, overexpression of CK2α leads to fewer cells in the G0 / G1 phase, whereas CK2 inhibition by CX-4945, K27, apigenin or CK2α siRNA led to increased apoptosis (Kim et al., 2007; Quotti Tubi et al., 2013). It has been reported that normal bone marrow cells are hardly affected by apigenin (Kim et al., 2007). Furthermore, the use of CK2 inhibitors or CK2α / β siRNA can sensitize AML cells to daunorubicin (AML chemotherapeutics) (Quotti Tubi et al., 2013).

In CLL, CK2 inhibition by CX-4945, DRB and TBB resulted in decreased cell viability without affecting normal T and B cells (Martins et al., 2010; Martins et al., 2014). Similar to ALL, primary CLL cells also showed up-regulation of phosphorylated PTEN. Knockdown or inhibition of CK2 increased expression levels of phosphorylated PTEN and PTEN (Martins et al., 2010). The CK2 inhibitor CIGB-300 also promoted the PTEN activation in CLL cells and terminated PI3K signaling pathway. Therefore, CIGB-300 decreases cell viability and proliferation in CLL cell lines, enhances apoptosis in primary leukemia cells, and showed anti-cancer activity in a human CLL xenograft mouse model (Martins et al., 2014).

In B-ALL cells, CX-4945 mediated inhibition of CK2 increased apoptosis in B-ALL cell lines and primary B-ALL cells but did not affect apoptosis in normal primary myeloid cells (Gomes et al., 2014). CX-4945 inhibited CK2-induced cell proliferation (Gowda et al., 2017). There are two possible mechanisms by which CX-4945 inhibits B-ALL: lowering levels of both total PTEN and phosphorylated PTEN (Gomes et al., 2014), and decreasing the phosphorylation of Ikaros, a tumor suppressor, thus restore the anti-leukemic function of Ikaros (Gowda et al., 2017). It is noteworthy that in both xenograft models of B-ALL cell lines and cell lines, CX-4945 inhibited leukemic cell growth and increased mouse survival (Gowda et al., 2017).

In T-ALL, the CK2 inhibitors CX-4945, TBB and DRB reduced primary T-ALL cell viability without affecting normal T cells (Silva et al., 2008; Buontempo et al., 2014). CX-4945 deterred tumor growth in T-ALL xenograft models (Buontempo et al., 2014). CK2 is overexpressed in T-ALL cell lines and is related to the increased activity of NOTCH1 and MYC. CX-4945 exerted pro-apoptotic effects on T-ALL cell lines and also promoted proapoptotic degradation of NOTCH1 in cells and decreased MYC transcription. Overexpression of CK2α in primary T-ALL cells correlated with PTEN phosphorylation, and inhibition of CK2 resulted in an increase in PTEN activity, therefore decreasing Akt phosphorylation (Kim et al., 2007; Silva et al., 2008; Martins et al., 2010; Piazza et al., 2012; Buontempo et al., 2014; Martins et al., 2014; Gowda et al., 2017). A recent study of CK2 in T-ALL showed that inhibition of CK2 induced apoptosis of T-ALL cells by regulating the endoplasmic reticulum stress (ER stress) / unfolded protein response (UPR) signaling pathway. CX-4945 down-regulated PI3K / Akt / mTOR signaling pathway, and might be effective in treating T-ALL diseases (Buontempo et al., 2014).

In conclusion, CK2 is overexpressed in many carcinomas and often associated with poor prognosis (but not in all cases). CK2 has been used as a diagnostic and prognostic marker for certain malignancies such as prostate carcinoma (Ortega et al., 2014; Qaiser et al., 2016). Further research about CK2 activity levels of all three CK2 subunits and their localizations may explore greater potential of CK2 as a diagnostic and prognostic marker. The mechanism of the increased CK2 RNA and protein levels in most carcinoma types is still unknown, while changes in gene dosage, epigenetic and post-translational regulation have been proposed. In some carcinomas the activity of CK2 is differentially displayed without changes in expression levels of CK2α / α’ (Trembley et al., 2012; Yoo et al., 2012), suggesting the existence of additional post-translational regulatory
mechanisms. CK2 protein is localized in nuclei of many tumor cells and correlates with clinical features in some cases. This suggests that the phosphorylation of target proteins in the nucleus is an important step for the CK2 function in carcinoma. However, we know little about CK2 nuclear targets.

CK2 has become a potential anti-carcinoma target. It has been studied in various tumors include lung carcinoma, head and neck carcinoma, cholangiocarcinoma, cervical carcinoma and multiple myeloma, etc. CK2 inhibitors are highly effective against solid tumors and in combination with other therapies for hematological malignancies. Among them, CIGB-300 is well tolerated in clinical trials of cervical carcinoma. CX-4945 is also well tolerated in Phase I trials conducted at the MD. Anderson Carcinoma Center in the United States, involving a variety of patients with advanced solid tumors and multiple myeloma. These two inhibitors can be used as a single agent for treatment, just as other signal transduction inhibitors in some carcinomas. They can also be used in association with radiotherapy or in combination with other therapies such as immunotherapy and other drugs such as JQ1. Combination therapy displays several advantages as it can enhance anti-proliferative effects, help to overcome the drug resistance and reduce the drug dosage which leads to fewer side effects.

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