Protein kinase 2 (CK2): a potential regulator of immune cell development and function in cancer

Kazim Husain, Tanika T. Williamson, Nadine Nelson and Tomar Ghansah

Department of Molecular Medicine, University of South Florida, Tampa, FL, USA

ABSTRACT
Protein kinase CK2, formally known as casein kinase II, is ubiquitously expressed and highly conserved serine/threonine or tyrosine kinase enzyme that regulates diverse signaling pathways responsible for cellular processes (i.e., cell proliferation and apoptosis) via interactions with over 500 known substrates. The enzyme's physiological interactions and cellular functions have been widely studied, most notably in the blood and solid malignancies. CK2 has intrinsic role in carcinogenesis as overexpression of CK2 subunits (α, α', and β) and deregulation of its activity have been linked to various forms of cancers. CK2 also has extrinsic role in cancer stroma or in the tumor microenvironment (TME) including the immune cells. However, very few research studies have focused on extrinsic role of CK2 in regulating immune responses as a therapeutic alternative for cancer. The following review discusses CK2's regulation of key signaling events [Nuclear factor kappa B (NF-κB), Janus kinase/signal transducer and activators of transcription (JAK/STAT), Hypoxia inducible factor-1alpha (HIF-1α), Cyclooxygenase-2 (COX-2), Extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), Notch, Protein kinase B/AKT, Ikaros and Wnt] that can influence the development and function of immune cells in cancer. Potential clinical trials using potent CK2 inhibitors will facilitate and improve the treatment of human malignancies.

1. Introduction
George Burnett and Eugene P. Kennedy were the first scientists discovered protein kinase 2 (CK2) approximately 65 years ago, when trying to evaluate an enzyme capable of the phosphorylation of a protein substrate by ATP [1]. Interestingly, the protein kinase was mistakenly named casein kinase II before it was later realized that caseins are only in vitro substrates; whereas, CK2 was initially detected in an animal model (in vivo). Further evaluation of the enzyme protein, throughout the years, would lead scientists to find that CK2 is composed of 2 catalytic subunits, CK2α and CK2α', and two regulatory subunits, CK2β, that has been identified in multiple forms [2]. Together, the isoforms create a tetrameric, holoenzyme complex with CK2α and/or CK2α' (42 and 38 kDa, respectively) linked to 2 CK2β subunits (28 kDa). CK2β has been proven to be the core of the protein structure due to its ability to stabilize/modulate CK2α subunits and plays an active role in cellular regulation [3]. Buchou et al. [4] performed in vivo experiments with CK2β knock out (KO) mice and in vitro experiments with embryonic fibroblasts depleted of CK2β to showcase the defects in cell proliferation and embryonic lethality that occur in the absence of the subunit. Similar results were reported with CK2α KO mice [5]. The following studies concluded that CK2β and CK2α play an essential role in the development and differentiation, most notably in vertebrates. CK2α KO mice, on the other hand, are still viable but produce sterile offspring, indicating its significant function in spermatogenesis [5–7]. Prior studies have even demonstrated that protein kinase CK2 subunits are able to functionally exist outside the confines of the holoenzyme [8]. The omnipresent enzyme protein undergoes dynamic shuttling between cytoplasmic and nuclear compartments as well as intracellular shuttling, which reinforces the ideology that CK2 plays a critical role in the regulation of diverse cell signaling responses [8–10]. More specifically, CK2 is a critical regulator for cellular development, proliferation, and survival [11]. Prior studies have also reported that the CK2 enzyme protein changes cell morphology, enhances cellular transformation, and promotes angiogenesis [12]. Interestingly, elevated levels of CK2 have been observed in malignant cells and are used to determine prognosis as well as survival in various forms.
of cancer (i.e., breast, prostate, ovarian, lung, colon, and pancreatic) [12]. Scientists have considered the option of using the kinase protein for targeted cancer therapy being that it is a potent suppressor of cell death (apoptosis), which is one of the hallmarks of cancer. Previous studies have successfully demonstrated inhibiting CK2 expression utilizing peptides, RNAi strategies, and other molecules leading to cancer cell deaths both in vivo (xenograft tumors) and in vitro [13,14]. The following review will evaluate the molecular mechanisms behind the CK2’s intrinsic role in solid tumors as well as in blood cancer. CK2’s extrinsic role to influence the immune cell development and function in the TME along with its ability to regulate inflammatory, oncogenic signaling pathways will also be explored. This comprehensive review of CK2 and its relevance to hematological and solid cancers may help lead to the development of new therapeutic regimens.

2. Influence of CK2 expression on cancer cells

Since CK2 is expressed in both normal and cancer cells, it was initially thought to be a marker of cellular proliferation [15,16]. Previous studies have subsequently proved that elevated levels of CK2 in the nucleus as well as its suppression of apoptosis and induction of dysplasia were specific to cancer cells [9,10,17–19]. In fact, upregulated CK2 protein expression has been observed in most of the tumors investigated [16,20], emphasizing its role in tumorigenesis. More specifically, overexpression of CK2 has been detected in breast, prostate, kidney, lung, head and neck, cervical, glioblastoma, ovarian, melanoma, bladder, mesothelioma, endometrium, gastrointestinal (i.e., biliary, liver, esophageal, gastric, colorectal, pancreatic and cholangiocarcinoma), as well as in blood cancers (i.e., myelomas, leukemias and lymphomas). Mechanistically CK2 regulates the activity of at least 15 cancer-related proteins specifically tumor suppressor TP53, the histone deacetylases HDAC1 and HDAC2, and nuclear factor-kappa B (NF-kB) subunit p65 [21]. The following section will discuss in detail the effects of CK2 expression in solid tumors and blood cancers.

2.1. Solid tumors

Elevated CK2 levels have been detected in the tumor microenvironment (TME) of both animal models and humans. Landesman-Bollag and colleagues [22] reported that dysregulated expression of CK2 is associated with and can contribute to tumorigenesis in the mammary glands of mice which resulted in hyperplasia and dysplasia with a marked percentage of mice developing spontaneous adenocarcinomas [22]. Overexpression of CK2α in the nucleus of human prostate cancer cells has been associated with unfavorable prognostic outcomes [23] and antisense CK2α caused the induction of apoptosis in a human prostate cancer xenograft mouse model [24]. Elevated CK2 activity was also observed in human renal cell carcinoma samples, which correlated with increased ratios of the α and β subunits in tumor versus normal tissues, at the protein level [25]. Additionally, increased CK2 activity has been detected in both the nuclear and cytosolic compartments of squamous cell carcinoma of the head and neck [26] and is associated with the aggressive nature and clinical outcome of the disease [27]. Similar findings were reported in squamous cell carcinoma of the lung [28] and larynx [29]. In human colorectal cancers, overexpression of CK2α in the nucleus is common and serves as a poor prognostic indicator due to its correlation with tumor invasion, stage, and other critical factors [30]. More recently, studies in glioblastoma multiforme (GBM), the most aggressive form of brain tumor, also showed elevated expression of CK2α [31]. Similar findings have been reported for the β regulatory subunit of CK2 in various malignancies. In gastric carcinoma patients, nuclear CK2β was overexpressed and correlated with poor overall survival rates [30]. CK2β is also frequently expressed in endometrial carcinoma, with significant increases apparent during the menstrual cycle in comparison to normal endometrium tissue [32]. This data supports previous findings of the inhibition of CK2 having anti-tumor effects in a mouse xenograft model of human glioblastoma [33].

CK2 activity has been implicated in the survival and resistance to apoptosis for the solid tumors. A number of in vitro as well as in vivo studies downregulating CK2 activity/expression using selective inhibitors, siRNA, antisense oligodeoxynucleotides, or kinase-inactive mutants of CK2 have shown that cancer cells heavily rely on CK2 activity/expression for survival [34]. This dependency or ‘addiction’ to CK2 for survival is also a common phenomenon in malignancies where increased CK2 activity has not necessarily been reported, including in osteosarcomas, ovarian carcinomas, hepatocellular carcinomas, cervical and pancreatic cancers [35]. More importantly, the increased susceptibility of many cancer cell lines to apoptosis as a result of inhibition of CK2 activity increases sensitivity to chemotherapeutic drugs [35,36]. For example, in human pancreatic cancer, RNA interference against the catalytic
subunits of CK2 increases sensitivity to gemcitabine-induced cell death [37]. Considering the fact that chemotherapy resistance is an impediment to successfully treating pancreatic and other aggressive cancers, these findings point to the potential of CK2 inhibitors in combination with traditional chemotherapy drugs/chemo-preventive agents as a novel treatment strategy to increase the efficacy of these drugs and susceptibility of cancer cells to apoptosis. The dependency of cancer cells on CK2 may be exploited to specifically target neoplastic versus normal cells.

2.2. Blood cancers

Consistent with studies in solid tumors, the overexpression of CK2 and its regulation of apoptosis also occurs in blood malignancies. Increased CK2 activity and protein expression have been detected in plasma cells of multiple myeloma patients compared to control subjects. In vitro inhibition of CK2 activity had a cytotoxic effect on multiple myeloma plasma cells and increased their sensitivity to the chemotherapeutic agent, melphalan [38]. In fact, CX-4945, a small molecule inhibitor of CK2 [39] has been tested in a Phase I clinical trial in patients that have relapsed, experienced refractory multiple myeloma or have advanced solid tumors. In human T cell acute lymphoblastic leukemia (T-ALL), activation of the PI3K/AKT pathway is attributed to reduced phosphatase activity of PTEN. This occurs when CK2 becomes overexpressed, which causes the Bcr-Abl to activate AKT via the phosphorylation of PIP2 and PIP3 (Figure 1(A)) [40–42] This chain of events then increases cell proliferation, survival, growth, and angiogenesis. Contrastingly, the inhibition of CK2 promotes death within the cell (Figure 1(B)). Overexpression of CK2 contributed to the development of T cell leukemia and lymphoma [40,42]. Kim et al. [43] studied elevated CK2 expressions in patients with acute myeloid leukemia and found it to be an unfavorable prognostic marker and therapeutic target for inducing cell death. Martins and colleagues [44] found similar results with chronic lymphocytic leukemia patients.

3. Inflammatory and oncogenic signaling molecules regulate immune responses through CK2 expression

As previously highlighted, several studies have investigated the role of CK2 in cancer. Very few of these have focused on CK2’s involvement in regulating immune responses in the tumor microenvironment (TME). It is well understood that CK2 regulates and interacts with oncogenes, tumor suppressors, and other important genes involved in various cellular processes (i.e., transcription, translation, chromatin remodeling, cell cycle progression, proliferation, survival, apoptosis, metastasis, invasion and control of protein stability and degradation). A number of these genes are also involved in key inflammatory signaling pathways that can influence the outcome of immune responses. However, the investigation of CK2’s contribution to these inflammatory signaling pathways, immune responses, and development of cancer is still not quite clear. CK2 regulates several oncogenic signaling pathways that

![Figure 1. Schematic depiction of protein kinase CK2-mediated signaling in chronic myeloid leukemia. (A) The Bcr moiety of Bcr-Abl interacts with and activates CK2 which then phosphorylates and inactivates PTEN. Bcr-Abl stimulates PI3K activity which catalyzes the conversion of PIP2 to PIP3. PIP3 has a pivotal role in Akt activation leading to enhanced cell proliferation, survival, angiogenesis and anti-apoptosis responses. (B) Treatment with CK2 inhibitors inhibits PI3K activity and PTEN dephosphorylates PIP3 to PIP2, leading to inhibition ofAkt activity. Inhibition of Akt activity results in the cell cycle arrest and induction of apoptosis. PI3K-phosphatidylinositol 3-phosphate kinase; PIP2-phosphatidylinositol 4,5-bisphosphate; PIP3-phosphatidylinositol 3,4,5-trisphosphate; PTEN- phosphatase and tensin homolog.](image)
Interestingly, several studies have demonstrated that CK2 downregulates the expression/activities of oncogenic signaling molecules such as NF-κB, COX-2, JAK/STAT and HIF-1α. CK2 also upregulates the expression/activities of oncogenic signalizing molecules such as AKT, Wnt and ERK. Interestingly CK2 downregulates the expression/activities of Notch and Ikaros as these molecules act as tumor suppressors.

can influence the activation, proliferation, survival, differentiation and function of immune cells. Many of these pathways are deregulated in immune cells and cancers suggesting the possible involvement of CK2 in these altered processes. To investigate this possibility, we summarized key inflammatory and oncogenic signaling molecules regulated by CK2 (Figure 2), and their specific roles in immune cell development and function (Table 1).

3.1. NF-κB

Nuclear Factor-kappa B (NF-κB) is an inflammatory transcription factor [45]. Several studies have shown that CK2 phosphorylation of IκB leads to IκB degradation and NF-κB activation independent of inhibitors of κB kinase (IKK) activity [46–48]. It activates several gene transcription involved in cellular processes [49], specifically immune cell development, inflammation, proliferation and apoptosis [50,51]. Interestingly, several studies have demonstrated that CK2 downregulates the functionality of NF-κB. Quotti Tubi et al. hypothesized that blocking both CK2 and NF-κB would increase the cytotoxic effect on leukemia stem cells [52]. In addition, CK2 activity results in the activation of NF-κB via its ability to phosphorylate the p65 subunit of the NF-κB dimer in response to IL-1 in hepatocytes as well as in fibroblasts [53] and controls TNF-α dependent phosphorylation of p65 [54]. CK2 phosphorylation and activation of NF-κB is also involved in NF-κB transcription of iNOS in response to IL-1 and LPS [55]. In intestinal epithelial cells, IL-1 stimulation leads to enhanced activation of CK2 bound to IKK or the p65 subunit of the NF-κB and inhibition of CK2 activity attenuated the expression of NF-κB-transcribed proinflammatory factors [56]. Therefore, CK2 regulation of NF-κB could influence its role in immune cells, which may contribute to the development of cancer. The inhibition of NF-κB through CK2 targets tumor not only directly by blocking anti-apoptosis mechanisms of malignant cells, but also indirectly by shifting macrophages from the tumor-tolerating M2-polarization stage towards the tumor-attacking M1-stage [57]. It should be noted that NF-κB also plays a primary role in hematopoiesis via the maturation of hematopoietic stem cells into functional immune cells utilized by both the innate and adaptive immune systems [58]. More specifically, the transcription factor is involved with the survival of dendritic cells and neutrophils during lymphopoiesis to regulate the proliferation and maturation of B and T cells. Additionally, NF-κB activation is important for macrophage viability and function in tumors [59,60]. Adaptive immune responses depend on NF-κB activation for toll-like receptor (TLR) pathway signaling. Proliferating T cells require NF-κB for pro-survival and cytokine production necessary for their proliferation and differentiation. For instance, NF-κB activation is essential for Treg differentiation [61]. It enhances the expression of cytokines (TNF-α, IL-1, IL-6 and IL-8), chemokines [chemokine (C-C motif) ligand 2 (CCL2)], adhesion molecules 1 (VCAM-1) and the Intracellular Cell Adhesion Molecule 1 (ICAM-1), matrix metalloproteinases (MMPs), cyclooxygenase 2 (COX2), inducible nitric oxide synthase (iNOS) and antiapoptotic protein (B-cell lymphoma 2) [62,63], all of which can influence leukocyte development, function and chemotaxis.

3.2. Janus kinase/signal transducer and activators of transcription (JAK/STAT)

JAK-STAT signaling is involved in the regulation of cell survival, proliferation, and differentiation [64]. JAK tyrosine kinases constitutively activated and phosphorylated STATs leading to regulation of the transcription of inflammatory cytokines as a result of mutations that affect their function in solid tumors and hematopoietic tumors [65–67]. CK2 binds to and phosphorylates JAK2 leading to activation of JAK/STATs signaling and induction of gene expression of proteins involved in growth, antiapoptotic mechanisms, angiogenesis, and immune evasion of tumor cells [67,68]. The inhibition of CK2 activity prevents cytokine-induced activation of JAK/STATs, inhibits downstream gene expression, and induces apoptosis in human erythroid leukemia (HEL) cells [68,69]. Each STAT family member protein plays a critical role in cytokine-dependent inflammation and immune modulation [67]. In the
Table 1. Summary of Immune cells whose development and function are regulated by CK2 signaling molecules.

| CK2 Signaling Molecules | Immune Cells |
|-------------------------|--------------|
| Nuclear Factor-kB (NF-kB) | Dendritic cells, Neutrophils, Macrophages, B cells, T cells |
| Janus Kinase/Signal Transducer and Activators of Transcription (JAK/STAT) | Macrophages, Dendritic cells, B cells, T cells |
| Hypoxia-Inducible Factor 1-alfa (HIF-1α) | Dendritic cells, Myeloid cells, B cells, T cells |
| Cyclooxygenase-2 (COX-2) | Dendritic cells, Myeloid cells, B cells, T cells |
| Extracellular Signal-Regulated Kinase (ERK) | Macrophages, Dendritic cells, B cells, T cells |
| Notch | Dendritic cells, Myeloid cells, B cells, T cells |
| AKT/Protein Kinase B | Dendritic cells, Macrophages, Myeloid Cells, B cells, T cells |
| Ikaros | Dendritic cells, Myeloid cells, B cells, T cells |
| Wnt | Dendritic cells, Macrophages, Myeloid Cells, B cells, T cells |

CK2 upregulates the expression/activities of NF-kB, JAK/STAT, HIF-1α, COX-2, ERK, AKT, and Wnt in immune cells whereas it downregulates the expression/activities of Notch and Ikaros in immune cells for their development and function.

TME, STAT proteins are the determining factor as to whether immune responses will act to promote or inhibit cancer progression via pathways regulating inflammation [67]. There is a cross talk between STAT3 and NF-κB and both cooperatively regulate anti-apoptotic, cell cycle, cytokines and chemokines genes in TME [70]. It has been shown that NF-κB interact physically with STAT3, facilitating NF-κB recruitment to STAT3 promoters and vice versa [70]. JAK3 is highly expressed in hematopoietic cells and is required for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine signaling; meanwhile, the STAT1 isoform is necessary for IFN signaling. These cytokines are critical mediators of lymphocyte development and function. JAK/STAT pathways play an important role in T cell lineage fates, particularly Th1 versus Th2. IL-4 stimulation causes STAT6 activation and the generation of IL-4 secreting Th2 cells, while IL-12 induces STAT4 activation resulting in IFN-γ-secreting Th1 cells [71,72]. In Tregs, STAT5 plays an important role in their development and function [73,74] and STAT3 regulates the generation of Th17 cells [74]. Furthermore, STAT3 is critical in generating effector B cells [75]. In dendritic cells, JAK3 is vital for their maturation, migration and function [76]. JAKS also modulate macrophage production of inflammatory cytokines [77]. STATs have been found to promote cellular proliferation and apoptosis resistance in human multiple myeloma cells and promote tumor tolerance by immune cells [78]. Since CK2 inhibition is associated with the impairment of STAT3 activation and signaling, a rational use of CK2 inhibitors would be together with STAT3 inhibitors. Therefore, CK2 and STAT3 inhibitors may cooperate in inducing antitumor immune responses. The combination of CK2 inhibitors with STAT3 inhibitors would likely to have synergistic antitumor activity and more efficacious for cancer immunotherapy.

3.3. HIF-1α

Hypoxia Inducible Factor (HIF) is a central transcription factor controls the cellular adaptation to a lack of oxygen or hypoxia [79]. Hypoxia occurs in most solid tumors due to inefficient vasculature and contributes to resistances observed in chemotherapy as well as radiation therapy [79,80]. CK2 activity and levels are elevated in hepatocellular and cervical cancer cells grown under hypoxia, concomitant with increased nuclear localization [81,82]. CK2 phosphorlylates HIF-1α and regulates its activity [81]. Hubert et al. [79], showed that CK2 may play a role in regulating HIF-1α as inhibition of CK2 activity resulted in decreased HIF-1α activity under hypoxic conditions through an increase in p53, a well-known CK2 target. This transcription factor potentially mediates inflammation via its regulation of hypoxia induction of NF-κB and its NF-κB-dependent activation by proinflammatory TNFα and IL-1β, in normoxic and cancer cells [83–85]. Changes in metabolism during inflammation can result in significant tissue hypoxia and thus, the induction of HIF-1α as well as hypoxia-responsive genes [86]. Direct transcriptional up-regulation of cyclooxygenase-2 by hypoxia-inducible factor (HIF)-1 promotes colorectal tumor cell survival and enhances HIF-1 transcriptional activity during hypoxia [87]. Mirzoeva et al. reported that CK2 inhibitor (Apigenin) inhibits hypoxia by disrupting the interaction between HIF-1α protein and HSP90 leading to suppression of prostate cancer angiogenesis [88]. Additionally, HIF-1α mediates leukocyte adhesion and myeloid cell infiltration at inflammatory sites [89,90]. When cells experience a deficiency in HIF-1α, it limits the development of B cells in the bone marrow and plays a crucial role for activating dendritic cells in inflammatory conditions [91,92]. HIF-1α also limits CD4+ and CD8+ T cell production of TNFα and IFNγ and their proliferation after T-cell receptor activation [93]. Our laboratory demonstrated that CK2 inhibitor (Apigenin) improves T cell homeostasis and function in murine pancreatic cancer [94]. Therefore, the association between HIF-1α, inflammation, immune modulation, and its regulation by CK2 should be further investigated.

3.4. COX-2

Cyclooxygenases-2 (COX-2) is a prostaglandin (PG)–endoperoxide synthase 2 enzyme responsible
for generation of prostaglandin E2 (PGE2) that is contributed to the modulation of pro-carcinogenic effects [95,96]. CK2 up-regulates COX-2 expression by modulating the Wnt/β-catenin signaling pathway and promotes the viability of human embryonic kidney cells [97]. Subsequent studies showed that CK2 was also a positive regulator of COX-2 dependent of PGE2 production, which correlated with increased viability of human colorectal and breast cancer cells [97]. CK2-dependent up-regulation of COX-2 expression is linked to the expression of cancer-related genes (AKT, β-catenin and survivin) as COX-2 is also a target of the Wnt/β-catenin pathway, a well-characterized substrate of CK2 [98]. Thus, CK2 inhibitors would be useful to inhibit COX-2 and oncogenic pathway leading to regression of tumor growth. Additionally, COX-2 is released by cancer-associated fibroblasts (CAFs), macrophage type 2 (M2) cells, Tregs and cancer cells to TME [96] and COX-2 mediated hypoxia within the TME along with its positive interactions with YAP1 and antiapoptotic mediators are responsible for cancer cell resistance to chemotherapeutic drugs [96,99,100]. Furthermore, enhanced COX-2 expression and its product PGE2 have been linked to immunosuppression in cancers due to the associated increase in IL-10, decrease in IL-12, IL-1 and TNF-α [57,96,101,102] as well as development of immunosuppressive MDSC and the induction of Tregs [103,104]. In CD8+ T cells, PGE2 accelerates their progression towards replicative senescence and their associated effector functions [96,105]. COX-inhibitors relieve the immunosuppressive effect of tumor cells and improve functions of immune effectors [99,100,106]. In summary, CK2 plays an important role in regulating COX-2 production of PGE2 in the TME due to its involvement in inflammation, immune cells and tumorigenesis. Therefore, the combination of CK2 inhibitors with COX-2 inhibitors would likely to have synergistic activity and more efficacious for cancer chemotherapy. Additional studies need to be done to confirm/elaborate this theory.

3.5. ERK/MAPK

Extracellular Signal-Regulated Kinase (ERK) is a member of the mitogen-activated protein kinase (MAPK) family downstream of the activated oncogenic RAS GTPase and activating mutations in these genes lead to oncogenesis and immune responses [106–109]. The Ras/Raf/MEK/ERK pathway is constitutively active in several cancers due to mutations in oncogenic RAS and signaling molecules [110]. CK2 is primarily responsible for phosphorylating ERK at its nuclear translocation signal allowing its nuclear import [111] and binding to transcription factors that induce gene expression cell proliferation, differentiation, apoptosis and tumorigenesis [112]. Elevated ERK expression has been detected in various human tumors, such as ovarian, colon, breast, lung and blood cancer [111,113–115]. The inhibition of CK2 is particularly potent in inducing apoptosis in HEL cells, which is associated with suppression of constitutive activation of ERK [111]. Additionally, ERK regulates the production of TNF-α and macrophage function [116]. The Activation of the ERK pathway is critical for T cell activation as well as in IL-2 expression and the differentiation of CD4+ T helper 2 (Th2) cells [117,118]. In dendritic cells, ERK regulates this suppressive function through Fas signaling [119]. ERK signaling also plays a role in B cell differentiation as well as macrophage differentiation and polarization [107,120]. The interaction between ERK and CK2 may therefore be important in regulating immune responses. Since CK2 inhibition is associated with the impairment of ERK activation and signaling, a rational use of CK2 inhibitors would be together with ERK inhibitors for synergistic effects.

3.6. Notch

Notch signaling pathway plays a vital role in transmitting and converting extracellular ligand signals into transcriptional responses in the nucleus [121]. CK2 has been demonstrated to be a regulator of the Notch pathway through the phosphorylation of Notch intracellular domain (NICD). Ranganathan et al. have identified multiple CK2 phosphorylation sites, located in the ankyrin domain of Notch. Phosphorylation of both sites resulted in decreased binding of NICD to DNA and consequently lower transcriptional activity [122]. Recently, researchers have established a relationship between the Notch signaling pathway and CK2 expression [123]. Notch1 protein levels were reduced after CK2 inhibition was silenced in cancer cells [123]. In addition, inhibition of CK2 using a small molecule inhibitor decreased Notch1 transcriptional activity and reduced the stem-cell like CD44+/CD24-cell population [124,125]. Notch activity, which inhibits the differentiation of MDSCs from hematopoietic stem cells and common myeloid progenitors, decreases with elevated levels of CK2 expression, a phenotype observed in cancer patients. This causes MDSCs, both monocytic and granulocytic, to accumulate in TME [126]. Cheng and colleagues [124] found that MDSCs from EL4 TB mice that have been transfected with control siRNA and cultured in tumor cell conditioned medium (TCM) had substantially lower Notch signaling (as measured by Hes1 expression) compared to cells cultured in
complete medium [127]. Similar results were observed for MDSCs transfected with CK2 siRNA and cultured with TCM. The study concluded that CK2 has a negative impact on Notch signaling, which contributes to increases in MDSC differentiation in the TME. Notch signaling is essential for T cell precursor and B cell development and differentiation. Thymus settling progenitors develop into several states of CD4+ and CD8+ double negative T progenitor cells that eventually differentiate into T cells with increased Notch activity [128]. Interestingly, Notch signaling is more likely to produce γδ T cells in humans and αβ T cells in mice. Previous studies have also shown that Notch activity promotes the differentiation of Th1, Th2, Th9, and Th17 through the up regulation of molecules such as SMAD3, Tbx2, and IL23r [128,129]. Notch signaling is required for T cell precursor and B cell development and differentiation. Notch also plays a role in dendritic cell development and maturation and myelopoiesis with altered Notch signaling contributing to MDSC development [129]. Notch signaling is also important for TCR-activation and peripheral T cell proliferation and the cytotoxic abilities of CD8+ T cells mediated by perforin and granzyme B expression. In addition, Notch activation regulates the differentiation of CD4+ T cells to Th1 vs Th2 cells by regulating the expression of key transcription factors and cytokines. Studies have also shown that Notch regulates CD4+ and CD8+ T cell cytokine production of IL-10 and IFN-γ and IL-17, respectively [130]. Increased CK2 activity and phosphorylation is also proposed to downregulate Notch signaling in hematopoietic progenitor cells and MDSC, emphasizing its role in myeloid cell differentiation [127]. CK2 downregulates Notch signaling in cancer cells and reduces a stem-cell like population in these cells [123–125]. Therefore, CK2 inhibitors are useful in combating the cancer progression by regulating the Notch pathway.

3.7. Protein Kinase B/AKT

Protein Kinase B (PKB or AKT), a serine/threonine kinase has diverse roles in cell proliferation, growth, survival, metabolism, angiogenesis, cancer, and immunity [131]. AKT is most frequently activated and overexpressed in solid tumors as well as in hematological malignancies and referred as oncopgenes [132]. CK2 has been shown to phosphorylate Akt at Ser 129 leading to its activation of downstream signaling events in various cell types [133]. Furthermore, the interaction between CK2 subunits and AKT enhance AKT’s activity [134,135]. Ruzzene and colleagues [135] demonstrated the relationship between CK2 and AKT. CK2 and AKT share global pro-survival and anti-apoptotic functions. Their activities are aberrantly high in human cancers, and their signaling pathways potentiate each other by several levels of cross-talk. Both α and β CK2 intervene in the direct binding to AKT resulting in an increased AKT activity. AKT signaling effects are mediated in conjunction with phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR). This PI3K/AKT/mTOR pathway is posed to be the most frequently activated pathway in human cancers with an occurrence rate of 30–50% [136]. Additionally, The PI3K-AKT pathway regulates both myeloid cells of the innate immune system and lymphoid cells of the adaptive immune system. In myeloid cells, AKT is activated by growth factors, cytokines (e.g., IL-4), and ligands for toll-like receptors (TLRs; e.g., LPS) and AKT activation stimulates a similar array of downstream effectors across the myeloid lineage [131]. AKT mediates macrophage polarization in response to different stimuli. M1 state is promoted by LPS, whereas the M2 state is induced by IL-4. Both M1 and M2 polarizing signals activate AKT and AKT signaling promotes M2 macrophage polarization [137]. In B and T cells, PI3K and mTOR regulate their cell survival, proliferation and B and T cell receptor signaling leading to their activation [138,139]. Similar regulation of survival and differentiation were found in dendritic cells [140]. In macrophages, AKT regulates inflammatory gene expression, their phagocytosis function as well as their migration and chemotaxis [141]. The PI3K/AKT pathway also controls the proliferation, survival, migration and metabolism of T cells [142]. AKT signaling also regulates the differentiation of effector and memory CD8 T cells [143]. The AKT/mTOR signaling pathway also modulates the differentiation of Th17 cells [144]. In regulatory T cells, the PI3K/AKT pathway is necessary for their proliferation and the inhibition of this pathway leads to their depletion in vivo [142]. Our group has published that MDSC have hyperactivation of AKT signaling, which may contribute to their expansion in pancreatic cancer [145]. Both CK2 and AKT phosphorylate each other leading to cellular synergistic effects. Therefore, both are attractive targets for therapeutic intervention of cancer.

3.8. Ikaros

Ikaros is a unique family of zinc finger transcription factors regulates normal hematopoiesis and is required for all lymphoid lineage development in which is critical for a functional immune system [146,147]. Ikaros knock-out mice lack B and T lymphocytes and natural killer (NK) cells, as well as
their defined progenitors [146]. Scientists have discovered that CK2 phosphorylates Ikaros in T cells, decreases its DNA-binding affinity for its target genes and re-distributes Ikaros protein in the nucleus from pericentromeric localization to a diffuse nuclear-staining pattern [148]. Lack of dephosphorylation of Ikaros by protein phosphatase 1 (PP1) leads to increased proteasomal degradation of Ikaros due to protein kinase CK2-mediated hyperphosphorylation at PEST regions [149]. Phosphorylation of Ikaros by CK2 regulates Ikaros binding and repression of the terminal deoxytransferase (TdT) gene in normal thymocytes and in T-cell ALL [150]. Overall, increased CK2 activity is thought to impede and/or downregulate Ikaros' function, causing malignant transformation [151]. Cho et al. investigated the possible involvement of CK2-regulation of Ikaros in inflammation by showing Ikaros phosphorylation by CK2 controls Ikaros' regulation of iNOS in response to LPS/IFN-γ stimulation in macrophages [152]. Furthermore, our recent findings also suggest a negative role for CK2 in regulating Ikaros stability in T cells to maintain effector and regulatory T cell homeostasis in murine pancreatic cancer [94]. Pancreatic tumor-derived factors (TDF) enhanced CK2 activity and inhibited protein phosphatase 1 (PP1) activity. CK2 hyperphosphorylated Ikaros leading to polyubiquitination and degradation by the ubiquitin-proteasome system and loss of T cell homeostasis in pancreatic tumor (Figure 3(A), modified from Nelson study) [94]. CK2 inhibitor apigenin (API) inhibited CK2 activity and stabilized Ikaros expression by increasing PP1 activity resulting in T cell homeostasis and anti-tumor immune response. Proteasome inhibitor MG132 directly inhibited activity of the ubiquitin-proteasome system and prevented the proteasomal degradation of Ikaros and thereby stabilized its expression (Figure 3(B), modified from Nelson study) [94]. Considering the evidence summarized in this review, it is possible that increased CK2 activity may be a result of proinflammatory stimuli affecting the downstream functions of Ikaros as a tumor suppressor. Thus, leading to tumorigenesis and deregulated expression of Ikaros-modulated inflammatory cytokines and genes; essentially resulting in altered immune cell development and function, further contributing to the observed cancer cell phenotypes.

3.9. Wnt

Wnt known as ‘Wingless-related integration site’ is a family of secreted cysteine-rich glycoproteins regulates cell proliferation, survival and fate determination [153]. CK2 function is required in Wnt

![Figure 3. Proposed model of Ikaros' regulation by CK2 in pancreatic tumor. (A) Pancreatic tumor-derived factors (TDF) enhanced CK2 activity and inhibited protein phosphatase 1 (PP1) activity. Enhanced CK2 activity hyperphosphorylated Ikaros leading to polyubiquitination and protein degradation by the ubiquitin-proteasome system. (B) CK2 inhibitor Apigenin (API) inhibited CK2 activity and stabilized Ikaros expression by increasing PP1 activity which resulted in T cell homeostasis and anti-tumor immune responses. Proteasome inhibitor MG132 in vitro directly inhibited the activity of the ubiquitin-proteasome system, prevented proteasomal degradation of Ikaros and stabilized its expression in pancreatic tumor microenvironment. Modified from Nelson study [94].](image-url)
producing cells for Wnt secretion [154]. CK2 is a positive regulator of Wnt pathway at multiple levels [155]. It phosphorylates intracellular Wnt signaling intermediates Dvl, β-catenin, and T cell-specific transcription factor/lymphoid enhancer-binding factor (TCF/LEF) [156]. Wnt signaling regulates the tumor-immune cycle in dendritic cells, T cells, and tumor cells. Increasing evidence suggests that Wnt signaling blocks the tumor-immune cycle at all steps, including tumor antigen release, antigen presentation, T cell priming and activation, T cell infiltration, and tumor cell elimination [157]. In the TME, activation of β-catenin depletes chemokine CXCL9/10 in CD103+ DCs and inhibits infiltration of effector T cells [158]. In addition, abnormal activation of Wnt signaling in DCs disrupts cross-priming of T cells by increasing the concentration of IL-10 [159]. Inactivation of Wnt signaling by deletion of Wnt receptor’s low-density lipoprotein receptor-related protein 5/6 (LRP5/6) in DCs facilitates tumor antigen capture and cross-priming, upregulates proinflammatory cytokines, and downregulates immune regulatory factors (IL-10 and TGF-β1), and eventually promotes T cell antitumor immune response [160]. Abnormal Wnt signaling directly alters several regulators critical for the antitumor activities of T cells, especially effector T cells, T helper cells, and regulatory T cells. Wnt signaling and TCF1 are required for generation of memory CD8+ T cells as well as generation and activation of CD8+ effector T cells [161]. Wnt signaling inhibits T helper (Th) cells and impairs antitumor immunity as well as the immunity of CD4+ T cells [162]. Wnt signaling, one of the best-characterized cancer drivers, have been tightly connected to the initiation and progression of many cancer type [158]. CK2-induced mammary tumors have upregulated nuclear β-catenin and CK2 inhibitors reduced proliferation and β-catenin expression in tumor cells [163]. Wnt signaling significantly activated in colorectal cancer and the antitumor immunity of CD4+ T cells is weakened by repressing IFN-γ expression and elevating IL-17a expression which can be involved in both pro-tumorigenic activity and in antitumor immunity [162]. Therefore, targeting Wnt signaling by CK2 inhibitors would potentially improve clinical outcomes of cancer patients by overcoming the primary, adaptive, and acquired resistance to immunotherapy.

3.10. CK2 inhibitors

With studies providing evidence that CK2 plays a critical role in cellular processes that lead to tumorigenesis, it is no surprise that emerging research has extensively focused on creating specific inhibitors of CK2. The CK2 protein’s ATP binding site contains unique bulky residues that favor the design of ATP-competitive inhibitors [164]. The most commonly studied inhibitors are CX-4945 ([5-(3-chlorophenyl)amino]-benzo(c)-2,6-naphthridine-8-carboxylic acid], CIGB-300, TBB (4,5,6,7-tetramorpho-bromo-1H-benzo[2,6]benzimidazole], DMAT (2-dimethylamino-4,5,6,7-tetramorpho-1H-benzoimidazole], Quinazilinarn, hematein, TBCA (Tetra bromo cinnamic acid], DRB [5,6-di-chloro-1-(b-D-ribofuranosyl)-benzimidazole], Apigenin (4’,5,7,tri-hydroxyflavone], Emadin (1,3,8-trihydroxy-6-methyl-antraquinone) and TF (6,7-dichloro-1,4-dihydrop-8-hydroxy-4-(4-methylphenylamino) methylene) dibeno [b, d] furan-3(2H)-one]. DRB, one of the first identified CK2 inhibitors, lacks the ability to inhibit other kinases with similar efficacy to CK2 [165,166]. Flavonoids, natural compounds found in fruit, vegetables, wine and tea, have also demonstrated the ability to inhibit CK2 activity. Two primary examples of flavonoids used for CK2 inhibition include apigenin and quercetin, both of which are more potent inhibitors of CK2 activity than DRB but maintain limited specificity [167]. Interestingly, apigenin is now characterized as a selective CK2 inhibitor with pro-apoptotic, anti-inflammatory, anti-cancer and chemopreventative effects. Another natural product shown to inhibit CK2 and other kinases with a broad specificity is emodin [168]. Currently, the most commercially available CK2 inhibitors are TBB and DMAT are specific to CK2 [164]. TBB is a derivative of DB while DMAT is a derivative of TBB’s analogue, TBI (Tetra Bromo-benzimidazole) [164,169,170]. IQA (5-oxo-5,6-dihydri-indolo(1,2-a) quinazolin-7-yl acetic acid), another CK2 inhibitor, shows enhanced selectivity and efficacy in vitro and in vivo compared to TBB, emodin and apigenin [167]. More recently, Cylene Pharmaceuticals developed the first orally bioavailable CK2 inhibitor called CX-4945 also known as Silmitasertib. This potent and highly selective, small molecule inhibitor blocks both CK2α and CK2α’ while causing cell cycle arrest, inhibition of cellular proliferation pathways and the promotion of apoptosis [171]. Interestingly, CX-4945 advanced to clinical trials in patients with solid tumors. Clinicians showed that the drug was well-tolerated with minimal side effects, inhibited CK2 and AKT pathways, caused a reduction in circulating tumor cells and IL-6 and IL-8 and stabilized disease in some patients [39]. CX-4945 also sensitized AML cells to daunorubicin (AML chemotherapeutics) and induced apoptosis of T-ALL cells by down-regulated PI3K/Akt/mTOR signaling pathway [40,172]. The second CK2 inhibitor known to have entered clinical trials (phases 1 and 2) is CIGB-300, a permeable cyclic peptide known to block CK2 phosphorylation by targeting specific phosphor acceptor domains [173]. Pre-clinical studies have also shown that Human H125 lung carcinoma cell lines treated with...
20 μM and 50 μM of CIGB-300 displayed significant reductions in tumor cell secreting enzymes, urokinase plasminogen activator and matrix metalloproteinase-2 [174]. 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 [175]. CK2 inhibitors (TBB and CX-4945) demonstrated a potent therapeutic effect in a panel of patient-derived primary high-risk B-cell acute lymphoblastic leukemia xenografts through prolonged survival and reduction of leukemia burden [151]. New CK2 inhibitors from Bristol Myers Squib company (BMS-211 and BMS-595) showed reduction in the number of PMN-MDSC and TAM by blocking of their differentiation in LLC lung, CT26 colon, 4T1 breast tumor-bearing mouse models [176]. Due to its positive response both preclinically and clinically, CIGB-300 is currently undergoing phase 3 for clinical trials most notably with patients involved with locally advanced cervical cancer. However, caution should be taken while using CK2 inhibitors in some cases. The clinical application of chemical inhibitors is not always the right strategy to target CK2 as CK2 functions, which are not dependent on its catalytic activity, but regulatory activity has also been reported [177,178]. The combination of CK2 inhibitors with other drugs might not be efficacious. In cases of melanoma and thyroid carcinoma, with WT BRAF, the efficacy of CK2 inhibitors in combination with BRAF/MEK inhibitors was poor [179]. Evidences also support a positive role of CK2 in allowing the cellular response to topoisomerase I-targeting drugs, in this case the combination therapy with CK2 inhibitors would be contraindicated [180,181]. Moreover, whether responsiveness to CK2 inhibition requires p53 functions, which would imply the inadequacy of CK2 targeting in case of TP53 mutation/deletion [31,172,182]. All these observations suggest that the clinical application of CK2 inhibitors should be carefully designed. CK2 is dispensable in the adult organism and in terminally differentiated cells, as inhibition of CK2 activity is not detrimental for the survival of normal cells [183]. CK2 inhibitor has been reported to inhibit the proliferation of chronic lymphocytic leukemia (CLL) cells without affecting the normal T and B cells [44,175,183]. Most importantly, the inhibition of CK2 may inhibit the self-renewal of the stem cell niche, which are also present in different tissues and organs of the adult organism and repair capacity of an organism. In summary, CK2 inhibitors are highly effective against solid tumors (breast, lung, head and neck, cervical, brain, ovarian, liver, and pancreas) and in combination with other therapies for hematological malignancies (Multiple Myeloma, Leukemia and Non-Hodgkin’s Lymphoma). Current and future clinical trials using CK2 inhibitors will be useful in combating this devastating disease in humans.

4. Conclusion

Regulation of signaling pathways that contribute to the development and function of immune cells is an area that requires further investigation. Our understanding as to the involvement of the diverse pathways in these processes as well as how they are connected, remains to be unraveled. CK2 has a clear, intrinsic role in providing a phenotypic advantage to cancer cells resulting in malignant transformation. However, in this review, we have summarized several findings that point to the possible extrinsic role of CK2 in regulating immune cell development and function via its regulation of inflammatory and oncogenic signaling pathways in cancer. Many of these pathways are tightly regulated during immune cell development. Therefore, alterations in their signaling mechanisms in tumor micro-environments can lead to diminished immune responses. Even with this understanding, targeting these signaling molecules with redundant and overlapping functions is a difficult task. Pursuing upstream regulators, such as CK2, are necessary for critical cellular functions, and can prove to be beneficial in controlling these molecular pathways. Furthermore, promising findings highlighted in this review provides evidence for the importance of developing highly specific and effective CK2 inhibitors. Overall, CK2 may serve as a potential therapeutic target for not only targeting tumors but also modulating inflammatory and oncogenic signaling pathways that influence immune responses. The omnipresence CK2’s involvement in diverse cellular processes makes it an attractive anti-therapeutic for restoring immune responses in solid and blood cancers. Potential future studies will hopefully provide an essential piece to the puzzle to our understanding of inflammation and its association with cancer as well as immunotherapeutic responses in preclinical and clinical investigations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability

We agree to share all the data and content of this review.
Author contributions
K.H., T.T.W., N.N., and T.G. conceived, planned, and wrote the review article.

Consent for publication
We consent to publication

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