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Protein kinase 2 (CK2) in carcinogenesis

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Abstract: The human kinase CK2 plays an important role in the physiological functioning of an eukaryotic cell, which is related to the regulation of the cell cycle, transcription, the DNA synthesis and repair, the mammalian circadian cycle and apoptosis. The activity of CK2 also involves the formation of pathological conditions in cells, which results, among others, with the involvement of the enzyme in the process of tumorigenesis. CK2 is a heterotetramer composed of two catalytic subunits such as CK2α and/or CK2α' and two regulatory subunits CK2β. It is significant that the subunits are functionally independent from the holoenzyme, showing the structural and functional diversity at the same time and other catalytic properties. The increased level of the enzyme activity was confirmed in all types of tumors and promotes tumor cell growth in several respects: stabilizes oncokinom, counteracts the effectiveness of anticancer drugs, promotes neovascularization and most importantly generates a wide spectrum of survival signals of cell. This is the reason of growing interest in the possibility of regulating its activity towards the design and synthesis of specific and potent inhibitors, what may result in obtaining specific antitumor drugs in the future.
Keywords: CK2; cancer; apoptosis, signaling pathways; anticancer therapy

1. Introduction

Phosphorylation is one of the most intensive post-translational protein modification processes. It is estimated that about 30% of the proteins in eukaryotic cells undergo reversible phosphorylation that can alter their functions, interactions, activity, localization, stability and affect to the key cellular regulation mechanisms such as cell cycle, p53 protein activity such as tumor suppressor, mammalian circadian rhythm and apoptosis [1÷5].

Due to the huge importance of protein phosphorylation in cells, the occurrence of protein kinases encoded by one of the largest eukaryotic gene families (about 2% of the genome) is common. In recent years 122 protein kinases genes have been identified in yeast cells, 540 in mice and 518 genes in the human genome, although according to estimates their number may be as high as 2000 [6÷9].

Kinase activity is precisely controlled and abnormalities in their functioning caused by i.a. mutations disturb the functioning of the whole signaling networks, leading to generation pathological and disease states. On the basis of the comparison of human chromosomal maps with identified disease *loci*, a direct contribution of 164 kinases to tumor formation was confirmed [10, 11].

2. General characterization of protein kinase II

The main element of regulatory and signaling networks based on protein phospho-rylation in the eukaryotic cell is the CK2 protein kinase (casein kinase 2 or II). It is a serine / threonine kinase that uses both ATP and GTP as phosphate residue donors. It is present in human cells most commonly in the form of a holoenzyme, a hetero-tetramer of approximately 130 kDa, consisting of two catalytic subunits α (42-44 kDa) and α '(38 kDa) and two regulatory subunits β (26 kDa), so it can exist in configu-rations α α'β_2, $\alpha_2\beta_2$ or $\alpha'_2\beta_2$ (fig.1) [12].

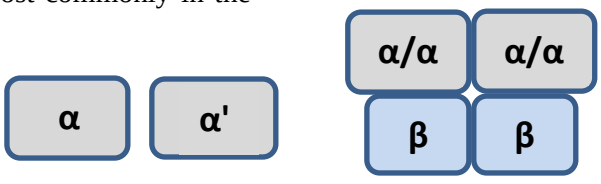


Figure 1. CK2 kinases can function as monomeric kinases and in a tetrameric complex [own elaboration].

The CK2 catalytic subunit consists of two characteristic domains: the smaller N-terminal and the larger C-terminal, which are connected by a single polypeptide chain (linker region), allowing free domain rotation upon binding of ATP and / or substrate. The phosphate donor binding site placed between the two main domains, interacts with the enzyme via

hydrogen bonds. The ATP binding site is characterized by the presence of five specific regions: three hydrophobic (adenine region, hydrophobic pocket I and II) and two hydrophilic (ribose region and phosphate binding region) that can be 4used to bind different chemical groups of inhibitors competing with ATP [13÷15].

The CK2β regulatory subunit in mammalian organisms is encoded by one gene and does not show sequential similarity to any other regulatory protein. Like the catalytic subunit, CK2β also consists of two domains. The N-terminal region represents a larger domain and has a α-helical character. This domain is associated with a smaller β structure (domain II), that contains a characteristic zinc ion group. The C-terminal loop (so-called tail) is directly involved in the holoenzyme formation. Catalytic subunits are attached to the regulatory subunits dimer and do not interact with each other. Each of the α subunits interacts with two β subunits [12, 14, 16, 17].

3. Cellular location, substrates and physiological importance of CK2

CK2 protein kinase is ubiquitous, pleiotropic and highly conserved enzyme in cells. It is widely located in *Metazoa*: plants, animals and humans. It has been also identified in primitive protozoa and in fungi representants [12, 18, 19].

In mammals, CK2 activity has been demonstrated in most tissues and almost in every cellular compartment, mainly in the nucleus, cytoplasm, cell membrane as well as mitochondrium membrane, mitochondrial matrix, endoplasmic reticulum, cytoskeleton, centrosome, Golgi apparatus and ribosomes [12, 19]. CK2 enzymatic activity in different cell compartments is variable and regulated in response to a variety of signals and impulse associated with cell cycle progression or cellular stress [20]. Moreover, nu-merous studies confirm the existence of catalytic and regulatory subunits independently of each other. Each of them can function separately, and their roles often remain different from the functions they perform in holoenzyme. Catalytic subunits preserve enzymatic activity and often is differ in substrate specificity. There is evidence of the dynamic localization of individual subunits and the independent displacement of α and β within the cell [12].

The presence of CK2 kinase in various cellular compartments is associated with the phosphorylation of many substrates and consequently the involvement of the enzyme in regulation of important cellular processes such as differentiation, mobility, cytoskeletal reorganization, proliferation, RNA synthesis, apoptosis and transformation [21].

So far, hundreds of physiological kinase substrates have been identified, and among them transcription factors (~ 60 proteins), proteins regulating the functions of nucleic acids and protein synthesis (~50), signaling proteins leaving out transcription factors (~90), cytoskeletal and structural proteins (~14). Approximately 40 substrates of CK2 were also identified among viral proteins [22].

Apart from the enzyme-substrate type connection, a number of CK2 interactions with non-substrate proteins have been described, which comprise one of the elements of CK2 activity regulation. This regulation takes place by the principle of interactions with the α (e.g. Pin1, APC, IRS-1, CKIP-1, PP2A, Grp94) or β subunit (e.g. $p21^{WAF1}$, p53, TNP-1, FGF-2) or both (e.g. Nopp140, eIF2β), the consequence of this is modulation of activity the subunits themselves or the whole holoenzyme [23].

Among the substrate proteins, both inhibitors (nucleic acid phosphoprotein Nopp140, translation initiation factor eIF2β, tumor suppressor p53), and activators of CK2 (e.g. HSP90 heat shock protein, nucleolin) were identified. Interactions with proteins regulating kinase activity may result in CK2 targeting to specific cellular structures, or modulating specificity for protein substrates (e.g. Pin1-reducing specificity for topoisomerase IIα, FACT – enhancing specificity for p53). So far, the contribution of 68 proteins to direct modification of CK2 activity has been confirmed [23÷25].

CK2 is an important element of every cell cycle step. In mammalian cells, its activity is crucial in the transition and progression G0/G1, G1/S and G2/M [26, 27]. Important elements of the cell cycle control, that remain under the control of CK2 kinase are among others: CAK kinase, p53 protein, SSRP1 proteins, FACT elongation factor element, MDM-2, $p21^{WAF1/CIP1}$, $p27^{KIP1}$, β-tubuline, Cdc25B, tau protein, PP2A, topoisomerase II, Chk1 kinase, CCdc34, Cdk1, Six1 and proteins associated with microtubules 1A and 1B [28]. The contribution of CK2 kinase to the Wee1 degradation pathway has also been

confirmed, and consequently its influence on the initiation of cell division [29].

CK2 is an important element of transcription control. The effects of the kinase activity involve multiple levels of regulation and a multitude of substrates. In particular, this regulation applies to the basic elements of the transcription mechanism, i.e the RNAP I, RNAP II and RNAP III polymerases [28].

Regulation of activity by phosphorylation or on the basis of other interactions with CK2 concerns also transcription factors: NFκB, STAT1, CREB, IRF-1 and IRF-2, ATF1, SRF, Max and protooncogenes: c-Jun, c-Fos, c-Myc and c-Myb [28].

Recently, the role of CK2 kinase in cellular processes that decide about cell entering the apoptosis pathway and the pro-life character of the kinase is the subject of intensive research. Overexpression of CK2 protects against drug-induced apoptosis and vice versa, kinase overexpression is often observed in cell lines that are resistant to apoptosis-inducing drugs. It is an enzyme directly involved in both types of pro-grammed cell death: extrinsic and intrinsic, induced by DNA damage, and inhibition of its activity induces apoptosis in tumor cells, which provides a promising aspect in cancer therapy [30÷32].

Many of the apoptosis signaling pathway proteins are direct substrates of CK2, others are regulated at the level of expression. One of the proteins is survivin, belonging to the group of apoptosis inhibiting proteins known as IAPs (Inhibitory Apoptosis Proteins), activity of which is inhibited by CK2 overexpression [33]. In turn, the phosphorylation of the Bid protein, a pro-apoptotic member of the Bcl protein family, protects it against caspase-8 activity, inhibiting mitochondrial apoptosis mechanism [34]. This type of regulation, where protein phosphorylation prevents caspase activity, indicates an evident antiapoptotic role of CK2. This phenomenon is determined by a similar sequence, rich in aspartate residues, recognized as a caspase cleavage site and simultaneously phosphorylated by CK2 [12]. A similar regulatory mechanism applies also to other caspase substrates: Max protein, HS1, presenilin-2, conexin 45,6 and PTEN [28]. CK2 also regulates the activity of caspases themselves. It has been proven that the caspase-9 phosphorylation in mice model protects it against caspase-8 activity, as well as the inhibitory effect of CK2 on caspase-2 dimerization and thereby its inactivation has been shown. Furthermore, the ARC protein, inhibiting caspase-8 activity, also remains under CK2 control [35÷37].

4. CK2 contribution in tumor processes

In addition to basic and key physiological functions, CK2 kinase is involved in the generation of many diseases, including neurodegenerative, viral, parasitic, inflammatory conditions and in many types of cancer.

CK2 level in cells remain at a constant characteristic level. It is relatively high in some organs such as in the brain or in the testicles, which represents a normal physiological condition. It rises during cell proliferation, whereupon it reaches a stable level that is crucial for cell homeostasis. Instead, in tumor cells elevated kinase activity is observed in the cell nuclei and deregulation of the kinase activity is observed in the disease intensification states, and it even serves as a prognostic indicator. Increased levels of the kinase activity is observed in all known types of tumors, including head and neck, kidney, colon, lung, prostate and breast cancer [38÷43].

High CK2 activity promotes tumor cell growth in a number of respects: a) improves transformation potential of oncogenes, b) stabilizes oncokinom by activation of co-chaperone CDC37, which is crucial for the maintenance of the active conformation of kinases with oncogenic potential, c) counteracts the effectiveness of anti-neoplastic drugs, especially imatinib and melphalan, d) promotes neovascularization, and most importantly e) generates a broad spectrum of pro-life cell signals [44].

Table 1. Known mechanisms by which CK2 plays a global role as a pro-survival and anti-apoptotic agent

CK2
Potentiates the Akt pathway
Promotes I κ B degradation and activates NF-kB
Stabilizes Dvl and β-catenin upregulating the Wnt pathway
Generates caspase resistant sites in Max, Bid, HS1, PTEN, connexin 45, caspase 9 etc.
Phosphorylates and activates the caspase inhibitor protein ARC
Promotes rRNA and tRNA biogenesis
Promotes the degradation of tumor suppressor PML
Facilitates DNA repair

Source: [44]

Many of these CK2 functions, particularly growth signals maintenance, apoptosis inhibition, involvement in angiogenesis lead to the changes in cell physiology characteristic for carcinogenesis.

Table 1 presents known mechanisms in which CK2 is involved, favoring the formation and maintenance of a neoplastic cell phenotype. In addition to the basic functions described in the previous chapter, i.e. participation in growth and proliferation regulation, rRNA and tRNA biogenesis, DNA repair, caspase inactivation, CK2 kinase also affects regulation of anti-apoptotic proteins and pathways, i.e. NF-κB, PI3'K / Akt and Wnt (Fig. 2, 3 and 4) [44].

NF-κB is a transcription factor involved in expression of cellular cytokines, cyclins D1, anti-apoptotic proteins (BcL-xI and IAP). It is usually located in the cytosol, where the interaction with an inhibitor IκB inhibits its activity. Degradation of IκB in the SCF-B-TrCP proteasome pathway releases the NF-κB factor, targeting it to the cell nucleus. CK2 works on several stages of this process. First and foremost, it activates IκB proteolysis, which constitutes an alternative pathway, alongside the basic IKK kinase-dependent pathway, expression of which is also under the control of CK2. Moreover, the p65 subunit of the NF-κB factor undergoes phosphorylation, which in turn increases its activity (fig. 2) [45, 46].

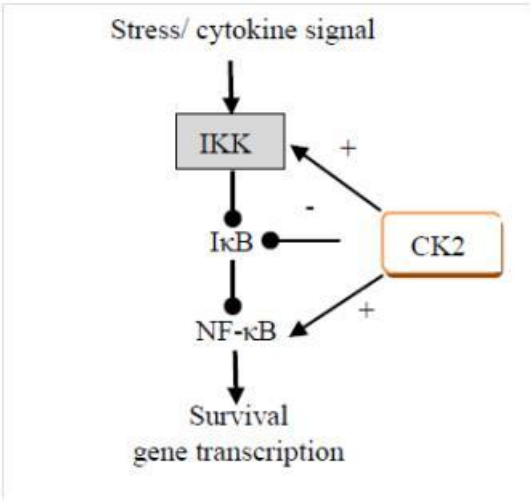


Figure 2. CK2-dependent multisite regulation of NF-κB. A negative effect (−) is indicated by a dot-arrow, and means inhibition or increased degradation, while a positive effect (+), indicated by a normal arrow, means enhanced stability and/or activity [44].

The Wnt signaling pathway plays an important role in embryogenesis, while its activity in adult individuals promotes transformation and carcinogenesis [47]. CK2 is involved in the reactivation of the pathway, which has been observed in case of colorectal cancer. The Wnt pathway regulates cell proliferation by maintaining a high level of β-catenin, which is a cofactor for a group of TCF / LEF transcription factors involved in expression of pro-life signals: c-Myc, c-Jun and cyclin D1. Phosphorylation of β-catenin by CK2 is a key element of the stabilization of this protein and of the protection against

proteasome degradation. The reverse effect is induced by phosphorylation of β-catenin by the GSKβ pathway kinase, which leads to ubiquitination and degradation of the protein. CK2 has also been shown to be involved in the phosphorylation of UBC3 and UBC3B proteins, which interact with the F-box, an element of the B-TrCP proteasome complex (fig. 3) [48, 49].

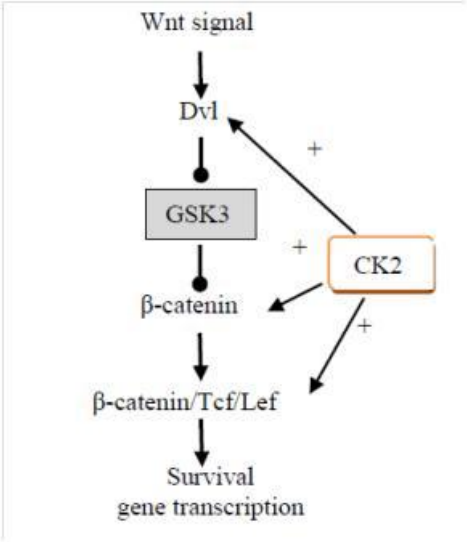


Figure 3. CK2-dependent multisite regulation of β-catenin. A negative effect (−) is indicated by a dot-arrow, and means inhibition or increased degradation, while a positive effect (+), indicated by a normal arrow, means enhanced stability and/or activity [44].

The contribution of CK2 in the stabilization and regulation of β-catenin level in the Wnt pathway also affects phosphorylation of Dvl proteins. These proteins are responsible for GSKβ activity regulation by blocking the ability of β-catenin phosphorylation, which in turn enables phosphorylation by CK2. As a result, dissociation of the protein from APC and Axin proteins, translocation to the nucleus and activation of pro-life signals take place [48].

The tumor suppressor – APC protein is a negative regulator of Wnt signaling, simultaneously interacting with CK2 via the α subunit and as a consequence it inhibits the activity mainly of the holoenzyme of the kinase. This effect achieves the highest level in G2 / M phase [40].

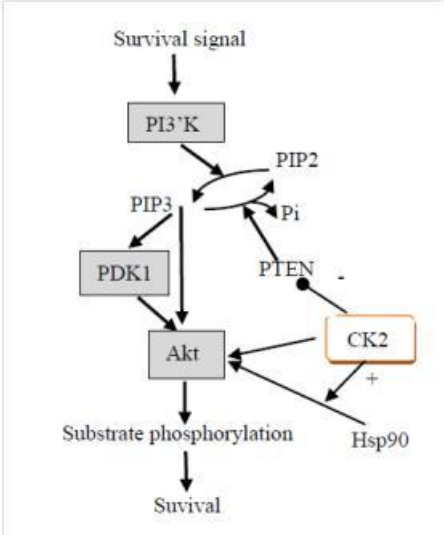


Figure 4. CK2-dependent multisite regulation of Akt. A negative effect (−) is indicated by a dot-arrow, and means inhibition or increased degradation, while a positive effect (+), indicated by a normal arrow, means enhanced stability and/or activity [44].

The effect of CK2 on cell survival is particularly visible in PI3'K / Akt pathway. The progression of the pathway is inhibited by PTEN phosphatase which dephosphorylates

phosphatidyl inositol 3,4,5-triphosphate (PIP3), acting antagonistic towards PI3'K kinase. The CK2-mediated PTEN phosphorylation inactivates this enzyme, which in turn stimulates Akt-dependent signaling. Interestingly, in most tumor cells PTEN activity is lost, whereas in T-ALL primary cells a high level of PTEN is maintained compared to normal T-lymphocytes precursors, which is simultaneously associated with high CK2 expression. Thus, the constitutive activity of the PI3'K / Akt pathway is possible not only in the inhibition of PTEN expression, but also in the inhibition of phosphatase activity by high CK2 level [44, 47, 50].

The direct effect of CK2 on Akt activity was also demonstrated by Thr-308 phosphorylation in the catalytic domain and Ser-473 in the C-terminal domain, as well as Ser-129 phosphorylation, which generates a constitutive kinase activity. CK2 contributes to maintaining a high level of Thr-308 phosphorylation, providing a stable connection with Hsp90 that protects Akt against dephosphorylation [51÷53].

Another mechanism by which CK2 affects the activity of tumor suppressor proteins is based on regulation of vulnerability to proteasome degradation. This type of regulation applies to i.a. PML protein involved in the control of many pathways responsible for growth inhibition, apoptosis or cell ageing. The loss of PML activity is observed in many cancers and correlates with the tumor progression. CK2 phospho-rylates PML at Ser-517, which is critical for directing the protein to degradation, and consequently protects cells against apoptosis [50].

The CK2 implication in signal cascades is often untypical in comparison with other kinases, primarily because it is not a component of hierarchical dependence, remains beyond the molecular regulatory mechanisms, simultanously integrates and consoli-dates the various connections and pathways. Hence deregulation of CK2 activity fosters such profound and diversified changes in cell biology.

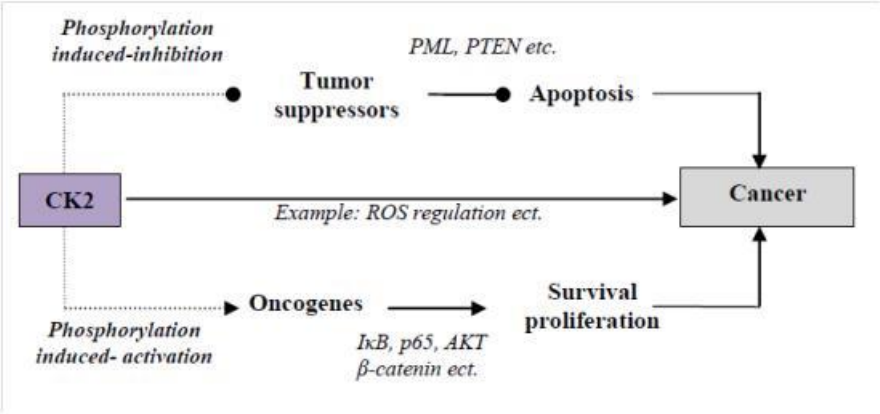


Figure 5. A schematic model for the role of CK2 in carcinogenesis. High levels of CK2 expression and activity have been illustrated in a variety of cancers [54].

Inhibition of CK2 activity by antisense RNAi, overexpression of inactive kinase form or chemical inhibition sensitizes cancer cells to induction of apoptosis by chemo- or radiotherapy. This dependence was confirmed and used i.a. in chemical induction of apoptosis in T-lymphoblastic cells or reactive oxygen species (ROS) dependent apoptosis in leukemia cells. The application of small interference RNAs in order to silence DNA expression supports therapy of rhabdomyosarcoma and colorectal cancer cells, making them sensitive to TNF-related apoptosis-inducing ligand (TRAIL) [54÷55].

Undoubtedly CK2 plays a significant role as an antiapoptotic and pro-life factor at many levels of its activity, as summarized in the figure 5.

5. Inhibitors of CK2

CK2 kinase is involved in many fundamental aspects of the physiological functioning of the cell, on the other hand promotes conditions conducive to carcinogenesis and other pathological conditions. Hence the growing interest in the possibility of regulation of its activity through the design and synthesis of specific and strong inhibitors, which in the

future may result in the acquisition of specific drugs.

5.1. ATP-competitive inhibitors

The human genome encodes more than 500 protein kinases, which are characterized by high conservative ATP binding site. However, there are some structural differences, mainly in proximally located regions, which generate the selectivity of ATP-competitive inhibitors. In *in vivo* studies, inhibitors often show a limited membrane permeability and a poor physiological effect. It is not without significance, that the cells exhibit high levels of ATP (1-10 mM), which is important primarily in inhibiting constitutively active kinases. In case of CK2, the high affinity of the enzyme to ATP also remains problematic [56].

There are several groups of chemicals that exhibit differentiated efficacy and specificity towards CK2. These are, i.a. the compounds of natural origin:

- flavonoids, eg. apigenin, quercetin, myricetin and fisetin;
- coumarins, eg. DBC (3,8-dibromo-7-hydroxy-4-methylchrom-2);
- antrachinons and xanthenones, eg. emodin (1,3,8-trihydroxy-6-methyl-antra-quinone), 1,3,8-trihydroxy-4-nitro-anthraquinone (MNA), 1,8-dihydroxy-4-nitro-xanthan-9-one (MNX) and 1,4-diamino-5,8-dihydroxyanthraquinone (DAA), quinalizarine (1,2,5,8-tetrahydroxy anthraquinone);
- ellagic acid;
- rezorufin [57÷59].

A significant group of competitive inhibitors against ATP are synthetic compounds:

- halogenated benzimidazole and benzotriazole derivatives, eg. DRB (5,6-dichloro-1-β-D-furanosyl-benzimidazole), TBB (4,5,6,7-tetrabromo-1*H*-benzotriazole) and its 2-dimethylamino derivative (DMAT), TBI (4,5,6,7-tetrabromo-1*H*-benzi-midazole), TIBI (4,5,6,7-tetraiodo-1*H*-benzimidazole);
- pyrazole-thiazine derivatives (according to PDB labeled 3BE9, 2PVH, 2PVJ, 2PVK, 2PVL, 2PVN);
- fluorenone derivatives such as FL12 (2,7-dihydroxy-3,6-dinitro-fluoren-9-one) and benzonaphthon derivatives eg. THN (tetrahydroxy-benzonaphthon);
- carboxylic acid derivatives, eg. IQA (5-oxo-5,6-dihydroindole- (1,2-a) -quina-zolin-7-yl-acetic acid), tetrabromic cinnamic acid derivative (TBCA), tribromic benzoic acid derivative and tetraiodic propionic acid derivative TID46;
- 3-carboxy-4-(1H)-quinolones, eg. 5,6,8-trichloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
- antimonic acid derivatives, eg, (*E*)-3-(3-antimonophenyl)-prop-2-enoic acid (IC_{50} = 0,15 μM);
- xanthene derivatives with negatively charged carboxyl or sulfonic groups, eg. 2,3,4,5-tetrabromo-6-6-hydroxy-3-oxo-3*H*-xanthen-9-yl-benzoic acid [57÷59].

Structures of selected inhibitors are shown in the figure 6.

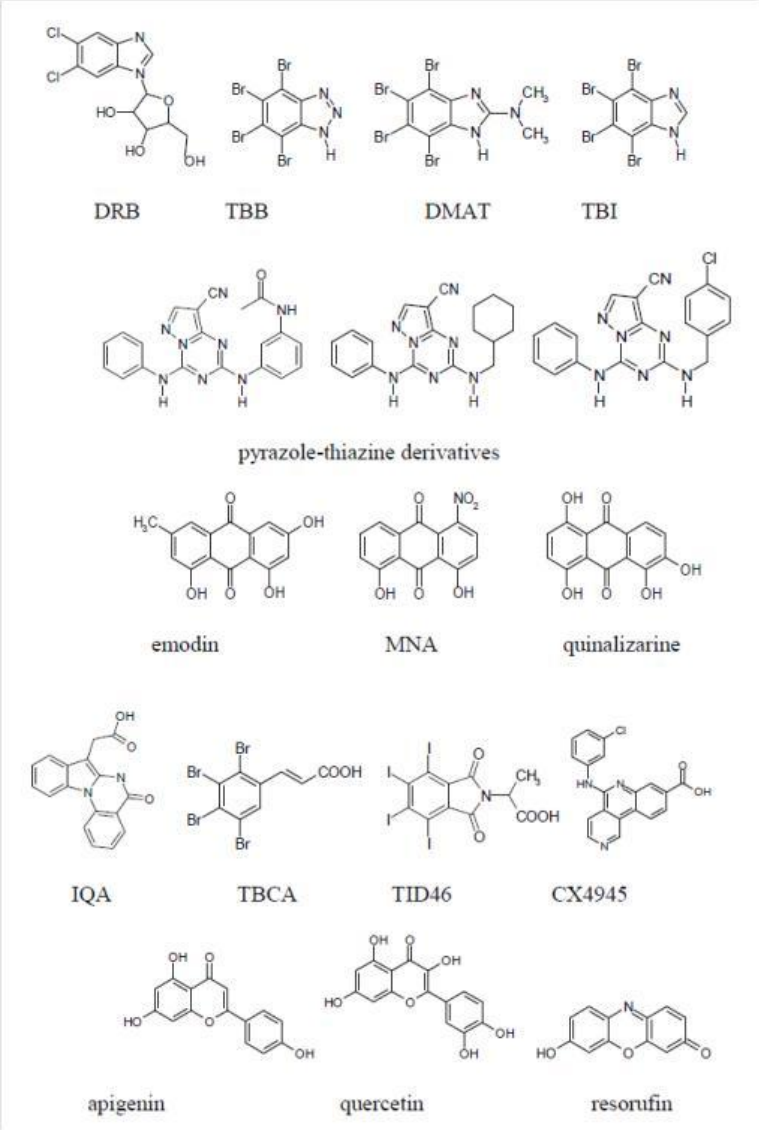


Figure 6. Chemical structures of selected ATP-competitive inhibitors of CK2 [own elaboration]

It is worth emphasizing that to this class of compounds belongs the first CK2 inhibitor which has successfully passed phase I of clinical trials, i.e. CX4945 (5-(3-chloro-phenylamino)-benzo-naphthyridine-8-carboxylic acid), also known as Sil-mitasertib. Activity tests performed on more than 145 kinases have confirmed its high selectivity for CK2. It shows a wide spectrum of antiproliferative activity on various cancer cell lines such as lung, breast cancer cells and prostate cancer. It has been demonstrated that the mechanism of antitumor activity of this compound is based on the inhibition of the processes in which CK2 kinase is involved, directly related to the maintenance of the tumor cell phenotype. This is an inhibition of the PI3K / Akt pathway by suppression of phosphorylation of Akt kinase and other key mediators such as p21 protein. Moreover, it selectively induces apoptosis in cancer cells and exhibits antiproliferative and anti-angiogenic effect. It is effective in the treatment of solid tumors and multiple myeloma, showing promising pharmacodynamic and pharmacokinetic properties. Currently CX-4945 is in phase I/II clinical trials in the United States, South Korea, and Taiwan for the treatment of cholangiocarcinoma in combination with gemcitabine and cisplatin (NCT02128282). The aim of this trial is to determine its maximum tolerable dose in patients followed by a randomized phase II assessment using CX-4945 in combination with gemcitabine and cisplatin versus the standard of care [60÷63].

5.2. Non-competitive inhibitors towards ATP

An alternative to ATP-competitive inhibitors are compounds that do not compete directly with ATP for active site, and inhibition of enzyme activity is based on a variety of mechanisms using structural and functional characteristics specific to CK2. These compounds generate less side effects and higher specificity of action mainly because of their targeting to less structurally conservative CK2 regions. Due to the fact, that they do not compete with cellular ATP, they can be used in concentrations close to biochemical K_i value. On the other hand, they are characterized by limit inhibition power resulting from low affinity and intracellular instability [64]. Examples of such inhibitors together with the mechanisms of their action are listed below:

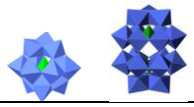
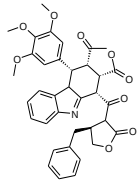
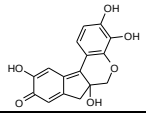
- polyanionic inhibitors (eg. heparin and other acid polysaccharides, eg. poly-glutamic acid and pseudo-substitutive peptides) interacting with a substrate binding site rich in base residues [59];
- CIGB-300 (phage cyclic P15 peptide formed after fusion with the cell penetrating Tat peptide), interacting with the phospho-receptor site of CK2 substrates, especially with B23 oncogene/ nucleoplasmin [65];
- inorganic ionic transition metal complexes, mainly tungsten, molybdenum and vanadium in the form of oxoligands (POM). The mechanism of action of these compounds is connected with the impact on the key structural elements of the enzyme, and in this case, the activation site blocks CK2 in an inactive conformation [66];
- peptide (P1) that interacts with the N-terminal domain of CK2β and blocks interactions between CK2β and specific ligands [67].

Structures of these inhibitors are shown in the table 2.

CIGB-300 is a second CK2 inhibitor tested in I/II Phase of clinical trials. In the clinical ground, this synthetic peptide has proved to be safe and well tolerated in a First-in-Human trial in women with cervical malignancies who also experienced signs of clinical benefit. In a second Phase I clinical trial in women with cervical cancer stage IB2/II, the MTD and DLT have been also identified in the clinical setting. Interestingly, in cervical tumors the B23/nucleophosmin protein levels were significantly reduced after CIGB-300 treatment at the nucleus compartment [68]. It should be noted that CIGB-300 modulates several CK2-dependent signaling pathways. In NSCLC models (non-small cell lung cancer), CIGB-300 induced an anti-proliferative response. This effect was accompanied by the inhibition of the NF-κB pathway, which was associated with an enhanced proteasome activity. Moreover, the NF-κB pathway appeared to be critically involved in the cisplatin-resistance of A549-cispR cells, which became more sensitive to CIGB-300 treatment [69]. Knowable data suggest a potential use of CIGB-300 as a novel therapeutic agent against lung cancer, because this peptide markedly decreased lung colonization and metastasis development of murine 3LL cells in mouse models and significantly reduced tumor cell-driven neovascularization [70].

CK2 is a very interested candidate for targeted therapy, with two inhibitors in ongoing clinical trials. CX-4945 is a bioavailable small-molecule ATP-competitive inhibitor targeting its active site, and CIGB-300 is a cell-permeable cyclic peptide that prevents phosphorylation of the E7 protein of HPV16 by CK2. In preclinical models, either of these inhibitors exhibit antitumor efficacy. Furthermore, in combinations with chemo-therapeutics such as cisplatin or gemcitabine, either CX-4945 or CIGB-300 promote synergistic induction of apoptosis [71].

Table 2. Non-competitive inhibitors with the mechanisms of their action.

Type of interaction	Type of molecule	Examples
Allosteric inhibitors	Inorganic compounds	POM 
CK2β binding inhibitors	Peptides	Peptide P1 GKMNGVLPLAWPSLYLRL
Inhibitors inhibiting interactions CK2α/CK2β	Cyclic peptide Organic compounds	Peptide Pc GCRLYGFKIHGCG W16 
Inhibitors inhibiting the attachment of a protein substrate	Cyclic peptide Organic compounds	Peptide P15 CWMSPRHLGTC Hematein 

Source: own elaboration

6. Conclusion

There is strong evidence that CK2 plays a role in the pathogenesis of cancer. CK2 is overexpressed in many cancers and often overexpression is associated with worse prognosis. CK2 is involved in many key aspects of cancer including inhibition of apoptosis, modulation of signaling pathways, DNA damage response, and cell cycle regulation. This enzyme has the ability to regulate signal transduction pathways, which may vary in different cancers, such as Wnt signaling, JAK/STAT, NF-κB, and PTEN/PI3K/Akt-PKB. Furthermore CK2 can be used as a diagnostic and prognostic marker in certain malignancies, such as prostate cancer.

The ability of CK2 to promote tumors causes the CK2 has emerged as a potential anticancer target. The wide range of cell-permeable chemical CK2 inhibitors have been developed. The most frequently used are TBB, quinalizarin, hematein, TBCA, CIGB-300, CX-4945, DRB, apigenin, DMAT, and emodin. Two of these CX-4945 and CIGB-300 have made into preclinical and clinical trials. These inhibitors are already used in phase I/II trials in certain malignancies like lung, head and neck cancer, cholangiocarcinoma, cervical cancer and multiple myeloma with promising results for the future.

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