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Focus on Molecules: Protein kinase CK2

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1. Structure/activity

CK2 (EC 2.7.11.1; formerly known as casein kinase II) is a highly conserved serine/threonine protein kinase expressed in all eukaryotic cells. CK2 is most often present as a tetramer composed of two catalytic (α and α′) and two regulatory subunits (β) (Fig. 1A). The two catalytic subunits, CK2α (42–44 kDa) and CK2α′ (38 kDa), in mammals are products of individual genes with more than 90% sequence identity in their N-terminal 330 amino acids, and entirely unrelated C-termini. A third catalytic isoform, CK2α″, recently discovered in human cells is practically identical to CK2α, except for the last 32 amino acids of its C-terminus. In contrast to the marked relationship of the catalytic subunits, the regulatory CK2β subunit (25 kDa) has no extensive similarity to other proteins. A consensus CK2 phosphorylation sequence contains acidic amino acids (Ser/Thr-X-X-Glu/Asp) and is distinct from those for other protein kinases (St-Denis and Litchfield, 2009). CK2 may also be a dual-specificity kinase as it can phosphorylate Tyr, although with much lower efficiency than Ser or Thr. CK2 is highly pleiotropic and appears to be capable of phosphorylating more than 300 substrates in all cellular compartments (Meggio and Pinna, 2003).

The regulatory CK2β subunit can control the catalytic activity of the enzyme at different levels. CK2β homodimer formation is required for incorporation of the catalytic subunits into the tetramer. CK2β is often required for recruiting and binding of CK2 substrates or regulators. Using yeast two-hybrid system, CK2β was shown to interact with at least 30 different proteins. Thus, CK2β appears to be mediating interactions between the catalytic subunit and its substrates, and modulating substrate selectivity and catalytic activity.

Recent data indicate that the holoenzyme formation is transient, as evidenced by the detection of free α and β subunits in mouse tissues, and by their differential subcellular localization and independent nuclear transport. In addition, free catalytic subunits can phosphorylate some substrates, for example calmodulin, only outside the tetramer.

CK2 is not only capable of phosphorylating target proteins, but itself is also subject to phosphorylation. CK2β is autophosphorylated following tetramer assembly at its N-terminal domain, which may regulate its proteasome-dependent degradation. C-terminal domains of CK2α and CK2β are also phosphorylated in a cell cycle-dependent manner by $p34^{cdc2}$.

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Many protein kinases require phosphorylation of certain sites in their activation loop to achieve full activation. However, phosphorylation of the activation loop of a CK2 catalytic subunit may not be necessary since the CK2 holoenzyme and its isolated catalytic subunits have constitutive activity in vitro without phosphorylation. Instead, the interaction between the N-terminal domain and the activation loop renders the isolated catalytic subunits constitutively active. The β subunit may help to stabilize this interaction.

2. Function

CK2 was found in various cellular compartments and appears to be involved in phosphorylation of a multitude of targets and regulation of a broad array of cellular processes, such as cell differentiation, motility, cytoskeleton reorganization, and proliferation. Cell cycle progression can be inhibited by antisense oligonucleotides against CK2α and CK2β, or by chemical inhibitors of CK2. Further evidence for a regulatory role of CK2 during cell cycle comes from the observations that in mitotic cells, phosphorylated CK2 subunits are associated with mitotic spindle and centrosomes, and that many cell cycle regulatory proteins are CK2 physiological targets, including cdc34 and topoisomerase II.

The significance of CK2 subunits as survival factors in mammalian cells has been demonstrated using mouse knockout models. Both the regulatory CK2β and the catalytic CK2α subunit knockout mice are embryonic lethal indicating that CK2β and CK2α are essential for viability and that CK2α′ cannot compensate for loss of CK2α. Interestingly, mice lacking the expression of CK2α′ are viable, although the male offspring are sterile. This defect is due to a highly elevated apoptosis in the germ cells of the CK2α′ null mice, implying a non-redundant role of CK2α′ in the survival of these cells. In mammalian cells, functional distinctions between CK2 catalytic subunits can also be substantiated by differences in phosphorylation, subcellular localization and protein partners. For example, CK2α is distinctively phosphorylated by $p34^{cdc2}$ at its C-terminal part in a cell cycle-dependent manner. This suggests that CK2α and CK2α′ are differentially regulated during the cell cycle. The identification of isoform-specific interacting proteins, such as molecular chaperone HSP90, PP2A (protein phosphatase 2A), and the peptidyl-prolyl isomerase Pin1 that all interact only with CK2α, provides further proof of functional differences between CK2 catalytic subunits.

Increased CK2 expression protects cells from drug-induced apoptosis, and conversely, CK2 inhibition activates apoptosis. One mechanism for protection is CK2-dependent phosphorylation of caspase-targeted proteins. Phosphorylation by CK2 of the caspase-targeted proteins, such as Bid, Max, or PTEN, at residues contained within caspase cleavage sites would protect them from caspase-mediated degradation and prevent apoptosis.

3. Disease involvement

Pathological conditions and in particular, tumor growth, are often caused by deregulation of protein kinases that get highly activated, often due to mutations. There are, however, no known mutations of CK2 found in tumors. For CK2, constitutive activity is an inherent feature that under certain conditions may cause cell transformation, and in fact, the levels of CK2 are elevated in many tumors. The causative role of CK2 in cancer has been confirmed by experimental CK2 overexpression in mouse models.

Elevated CK2 activity may promote tumorigenesis in many ways. CK2 can regulate the activity and stability of tumor suppressor proteins (p53, PTEN, PML) or promote cell survival through the regulation of proto-oncogenes (c-Myc, c-Myb, c-Jun) and transcriptional activators (β-catenin, NFκB, Max). Also, CK2 phosphorylates Akt at Ser129, which promotes cell viability by producing a constitutively active form of Akt that is a key

mediator in the PI3 kinase pro-survival signaling pathway. Thus, CK2 appears to be a potent anti-apoptotic factor that may provide specific environment favorable for transformation (Trembley et al., 2009).

Hypoxia can activate CK2, which positively regulates hypoxia-inducible factor-1α (HIF-1α) transcriptional activity targeting cell survival genes. A hypoxia-induced pathological condition is retinal neovascularization (RNV), a common diabetic complication. RNV can be promoted by pathological factors that act via multiple signaling pathways, including those regulated by Akt and CK2, which may increase survival of retinal vascular endothelium. In fact, CK2 can regulate many key signaling mediators of angiogenic growth factor action (Fig. 1B). Interestingly, a specific CK2 inhibitor partly blocked RNV in the mouse oxygen-induced retinopathy model, and its combined administration with somatostatin, another anti-angiogenic agent, reduced RNV even more (Kramerov et al., 2008). CK2 inhibition could also block engraftment of circulating endothelial progenitor cells into hypoxia-induced retinal neovessels (Kramerov et al., 2008) suggesting that CK2 can play a role in pathological retinal angiogenesis.

4. Future studies

Knowledge of CK2 regulation is crucial for understanding its physiological roles and for evaluating the prospects of using CK2 as a therapeutic target. Functional studies using CK2 inhibitors have provided important information on the involvement of CK2 in sensitizing cancer cells to standard treatments. Future approaches for fighting cancer or pathological neovascularization, could depend either on blocking some master modulators, such as HIF-1α or CK2, or on combination treatment inhibiting several targets simultaneously.

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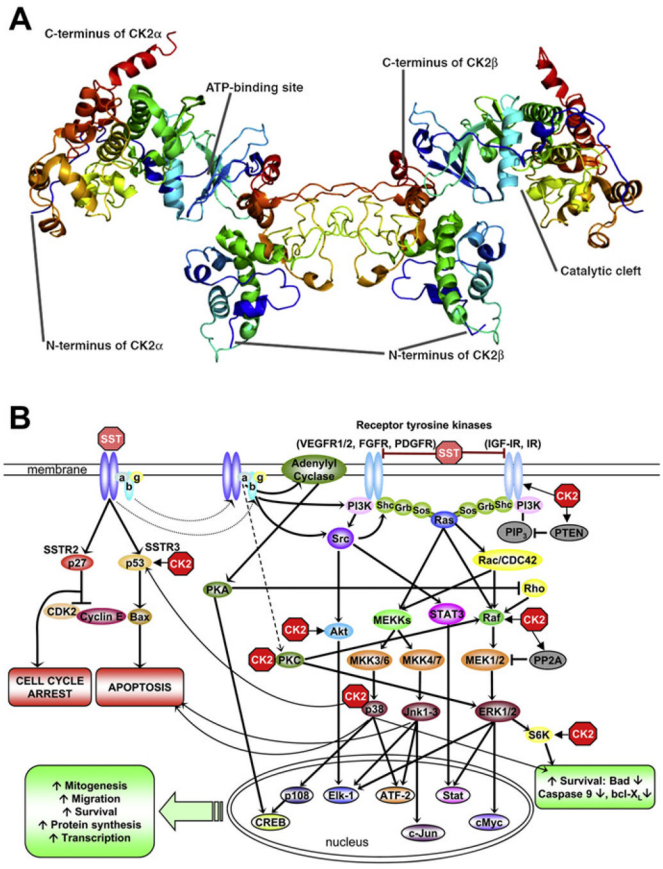

Fig. 1.

A – Structure of human CK2 holoenzyme. The CK2β homodimer is at the core of the tetramer complex bridging the two catalytic subunits (adapted from http://en.wikipedia.org/wiki/Casein_kinase_2,_alpha_1; based on Niefind, K., Guerra, B., Ermakowa, I., Issinger, O.G., 2001, EMBO J. 20: pp. 5320–5331). B – Schematic of signaling from angiogenic growth factors (VEGF, FGF, PDGF, IGF) and somatostatin (modified from Kramerov et al., 2008; Fig. 4, with kind permission from Springer Science + Business Media B.V.). CK2 and somatostatin (SST) modulate several major signaling pathways: Raf-ERK-S6 K, p38 MAPK and Akt, or p27, STAT3 and PKA, respectively. Together, they can influence a wider array of signaling pathways, which may allow for utilizing them for combination therapy of abnormal RNV.