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# Protein Kinase CK2 - A Key Suppressor of Apoptosis

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### Keywords

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## Introduction

In recent years, evidence has mounted in support of the importance of protein kinase CK2 (previously called casein kinase 2 or II) (EC 2.7.11.1) in diverse biological processes, and in particular in regard to its role in cell growth and proliferation in normal and disease states. In particular, emerging data have underscored a novel function of CK2 as a potent suppressor of apoptosis. Thus, it now appears that CK2 has a dual role in cell function, namely its involvement in growth and proliferation as well as in suppression of apoptosis. The latter function of CK2 is of particular significance with respect to its role in neoplasia since CK2 has been found to be consistently elevated in cancer cells which are known to demonstrate remarkable resistance to death. In this review, we have focused on the pertinent observations that implicate CK2 to have a global role as a suppressor of apoptosis and its relevance to the cancer phenotype.

## General Characteristics of Protein Kinase CK2

CK2 (official *acronym* for the former name casein kinase 2 or II) (EC 2.7.11.1) is a ubiquitous protein serine/threonine kinase that is among the most highly conserved proteins in nature. A unique property of this kinase is that it can utilize both ATP and GTP as substrates. Its heterotetrameric structure consists of two catalytic subunits (42 kDa α and 38 kDa α′) and two regulatory subunits (28 kDa β) existing as $\alpha_2\beta_2$, or $\alpha\alpha'\beta_2$, or $\alpha'_2\beta_2$ configurations. The two catalytic subunits are linked through the β subunits (Graham *et al.*, 2000). The β subunits in turn may form a linkage with the nuclear matrix (Zhang *et al.*, 1998) which is a key locus for CK2 signaling in the nucleus (Ahmed, 1999). The growth related functions of CK2 accord with CK2-mediated phosphorylation of a rather large number of substrates in the cell, many of which are nuclear-associated and are involved in gene expression and cell growth (for recent reviews see e.g., Guerra and Issinger, 1999; Ahmed *et al.*, 2000; Tawfic *et al.*, 2001; Ahmed *et al.*, 2002; Pinna, 2002; Litchfield, 2003; Pyerin and Ackermann, 2003). The kinase is localized to

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both the nuclear and cytoplasmic compartments in the cell, and undergoes dynamic shuttling between various compartments which may relate to its functional activity in those compartments (Ahmed *et al.*, 1993; Tawfic and Ahmed, 1994a, 1994b; Tawfic *et al.*, 1996, 1997; Guo *et al.*, 1998, 1999a, 1999b; Ahmed *et al.*, 2000; Faust and Montenarh, 2000). A key feature of CK2 cell biology is that it is essential for cell survival (e.g., Padmanabha *et al.*, 1990), and accordingly, attempts to produce CK2-knockout mice have been unsuccessful (Bouchou *et al.*, 2003).

The nature of existence of CK2 subunits in the cell is a subject of current investigations which have demonstrated divergent results (e.g., Guerra *et al.*, 1999; Martel *et al.*, 2002; Salvi *et al.*, 2006). Regulation of cellular CK2 appears to be complex and various hypotheses have been proposed on this subject (for reviews, see e.g., Allende and Allende, 1995; Ahmed, 1999; Montenarh and Faust, 2000; Pinna, 2002; Filhol *et al.*, 2004; Olsten *et al.*, 2005). To explain some of our data on CK2 responses to altered cell growth, we originally proposed that CK2 undergoes dynamic shuttling between cytoplasm and nucleus and further within the nucleus it undergoes differential distribution depending on the conditions to which the cell is exposed (Ahmed *et al.*, 1993; Ahmed, 1999; Tawfic and Ahmed, 1994a, 1994b; Tawfic *et al.*, 1996, 1997; Guo *et al.*, 1998, 1999a, 1999b; Ahmed *et al.*, 2000). Subsequently, it was demonstrated that CK2 translocation can take place to other parts of the cell further reinforcing the notion that dynamic intracellular shuttling of CK2 might represent a key mode of its regulation in the cell in response to diverse signals (Tawfic *et al.*, 1997; Faust and Montenarh, 2000). Analogous to these considerations is the emerging view that spatiotemporal organization of individual CK2 subunits in living cells involves multimolecular assemblies (Filhol *et al.*, 2004), and that association of discrete subpopulations of CK2 may be regulated independently (Olsten *et al.*, 2005). In this context, it is noteworthy that molecular downregulation of CK2 (e.g., by treatment of cells with antisense CK2 ODN) in cell culture or in vivo demonstrates a distinct reduction in the signal in the nuclear fractions such as chromatin and nuclear matrix (Faust *et al.*, 2000; Wang *et al.*, 2001; Slaton *et al.*, 2004).

## CK2 and Cancer

Much evidence exists supporting that CK2 signal is dysregulated in all the cancers that have been examined (for reviews, see e.g., Guerra and Issinger, 1999; Tawfic *et al.*, 2001; Wang *et al.*, 2006b). Interestingly, it appears that CK2 by itself is not oncogenic but rather it co-operates with other molecules thereby altering the oncogenic potential in the cell. Experimental transgenic mouse models of neoplasia in which altered CK2 signal served as a double transgene have provided significant support to this notion (e.g., Kelliher *et al.*, 1996; Xu *et al.*, 1999). The presence of elevated CK2 in cancer appears to correlate with the pathological status of the cancer and may serve as a prognostic marker (Yenice *et al.*, 1994; Gapany *et al.*, 1995; Faust *et al.*, 1996; Faust *et al.*, 1999; Piazza *et al.*, 2006; Laramas *et al.*, 2007). Although CK2 is present ubiquitously in all cells, it is noteworthy that its distribution in the normal versus cancer cells is distinct. In normal cells CK2 is localized in a diffuse pattern in the nuclear and cytoplasmic compartments whereas in cancer cells its distribution is characterized by a higher level in the nuclear compartment (Faust *et al.*, 1999; Laramas *et al.*, 2007). As indicated above, this difference in the localization of CK2 depending on the nature of the cell may be significant in regard to its function in cancer. Originally, it was unclear as to how elevated CK2 was involved in cancer cell biology considering that its activity is high in normal rapidly proliferating cells. This raised the question if CK2 increase in cancer cells was simply a reflection of their high proliferation. However, a comparison of CK2 immuno-reactivity with that of Ki-67 in the same tumor section revealed that both Ki-67 and CK2 signals were apparent in the proliferating edge of the tumor but the CK2 signal was additionally widely distributed in various cells in the section. This observation suggested that CK2 signal is not simply a proliferation marker but rather reflects the pathological status of the cell (Faust *et al.*, 1999),

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and is further supported by recent immunohistochemical analysis of prostate cancer specimens (Laramas *et al*., 2007). Additionally, as discussed subsequently, our demonstration that CK2 is a potent suppressor of apoptosis (Ahmed *et al.*, 2002) provided a novel link of CK2 function in cancer cell biology since it is well known that cancer cells not only demonstrate dysregulated growth but also dysregulated cell death. Thus, consistently elevated CK2 signal would not only contribute to altered cell growth and proliferation in cancer cells but also to suppression of cell death related activities.

## CK2 and Cell Death

Cell death is a complex phenomenon involving a variety of mechanisms. Of these, apoptosis (or programmed cell death) has gained considerable attention in regard to its potential significance in cancer cell death since it appears that dysregulation of apoptotic activity in cancer cells is an important feature of the cancer phenotype. Indeed, in certain cases, it may be even more significant than the dysregulation of cell growth (e.g., in the case of prostate cancer) (Kyprianou *et al.*, 2000). Apoptosis in cells can be induced by a variety of means including, e.g., removal of growth and survival factors from the cells, treatment of cells with chemical agents, or treatment of cells with ligands for death receptors. We have investigated the involvement of CK2 in modulation of apoptosis induced by these various mechanisms.

One of the first studies on nuclear-associated protein kinase activity towards acidic nonhistone proteins employing the experimental model of rat ventral prostate subjected to altered androgenic status demonstrated that removal of the androgenic stimulus resulted in loss of phosphorylation of these proteins in the prostate which was very rapidly reversed in response to androgen administration in the animal (Ahmed and Ishida, 1971). Subsequently, we identified CK2 to play a significant role in phosphorylation of certain of these nuclear proteins (Goueli and Ahmed, 1991; Tawfic and Ahmed, 1994a, 1994b; Guo *et al.*, 1998, 1999b); the variety of substrates of CK2 has expanded over time through investigations in various laboratories (for a review, see e.g., Meggio and Pinna, 2003). Our studies originally demonstrated that removal of the growth factor stimulus in the prostate gland (such as by androgen deprivation in the animal) resulted in rapid loss of nuclear CK2 such that it preceded the induction of apoptosis in prostate epithelial cells under these conditions. On the other hand, when growth stimulus was instituted by androgen administration in animals previously deprived of androgens there was a rapid shuttling of CK2 to the nuclear compartment of prostate epithelial cells prior to cell growth. Noteworthy was the observation that the translocated CK2 was differentially associated with the chromatin and nuclear matrix fractions in the nucleus (Ahmed *et al.*, 1993; Tawfic and Ahmed, 1994b; Guo *et al.*, 1998; Ahmed, 1999; Tawfic *et al.*, 2001). Removal of growth factors from the culture media resulted in shuttling of CK2 from the nuclear to the cytoplasmic compartment and subsequent addition of the growth factors to the culture media demonstrated a reversal of this process with CK2 shuttling to the nucleus (Guo *et al.*, 1999a). Further corroborative support for these considerations has been provided by recent documentation that nuclear accumulation of PTHrP (a key survival factor for cells subjected to apoptotic stimuli) effectively inhibits mitochondrial-mediated apoptosis through regulation of the expression, activity and sub-cellular trafficking of CK2 (Okoumassoun *et al.*, 2007). Together, these observations point to a correlation of loss of nuclear CK2 to induction of apoptosis in response to removal of survival or growth factors whereas the reverse was the case upon administration of survival or growth factors. Thus, our observations provided the initial indication that dynamic changes in CK2 (especially in the nuclear compartment) play important role in cell growth and in cell death (Ahmed *et al.*, 2000; Yu et al., 2001).

Further investigations of the involvement of CK2 in chemical mediated apoptosis demonstrated that treatment of cells with chemical agents such as etoposide and diethylstilbestrol which are well known chemical mediators of apoptosis caused an initial rapid shuttling of CK2 to the

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nuclear compartment presumably as a survival response of the cells. To provide a more direct confirmation of the role of CK2 as a suppressor of apoptosis we demonstrated that forced overexpression of CK2 prior to treatment of cells with etoposide or diethylstilbestrol strongly protected them against apoptosis (Guo *et al.*, 2001). Analogous observations based on heat shock treatment of cells supported the role of CK2 in promoting cell survival (Ahmed *et al.*, 2002; Davis *et al.*, 2002), and subsequent studies employing radiation or UV treatment of cells have made similar observations (Kato *et al.*, 2003; Yamane and Kinsella, 2005). It was previously suggested that CK2 may be involved in phosphorylation of ser-392 induced by UV damage of DNA (Keller *et al.*, 2001). Recent documentation that CK2 mediates DNA repair following single strand damage (Loizou *et al.*, 2004) may also be pertinent to regulation of cell death. Thus, it appears that CK2 impacts on apoptotic activity in cells mediated by chemical agents and also by physical stress.

An important means of induction of apoptosis in cells is *via* activation of the death receptor pathway. We and others have investigated the relationship between this mode of apoptosis and CK2, leading to the demonstration that CK2 impacts on apoptosis mediated by TNF-α, TRAIL, and FasL which bind to their cognate death receptors in prostate cancer cells (Wang *et al.*, 2005a; Wang *et al.*, 2006a) and other cancer cells (Ravi and Bedi, 2002; Izeradjene *et al.*, 2005). To that end, we observed that when CK2 is moderately downregulated (by employing relatively low levels of chemical inhibitors of CK2 such as 4,5,6,7-tetrabromobenzotriazole (TBB) or apigenin or by molecular downregulation employing antisense CK2 or siRNA) there was a remarkable sensitization of cells towards death receptor ligands which under these conditions induced cell death at sub-optimal concentrations. Forced overexpression of CK2 impeded the effectiveness of the death receptor ligands in inducing apoptosis (Wang *et al.*, 2005a; Wang *et al.*, 2006a).

We originally demonstrated that treatment of cancer cells with antisense CK2 (or CK2 siRNA) resulted in potent induction of apoptosis (Faust *et al.*, 2000; Wang *et al.*, 2001; Ahmad *et al.*, 2006). The induction of apoptosis was apparent when CK2 activity was reduced by 30–40% in the nuclear compartment (chromatin or nuclear matrix) (Faust *et al.*, 2000; Wang *et al.*, 2001). Recent studies by us (Wang *et al.*, 2005b; Wang *et al.*, 2006a; Ahmad *et al.*, 2006; Ahmad *et al.*, 2007) and by others (Ruzzene *et al.*, 2002; Seeber *et al.*, 2005; Pagano *et al.*, 2007; Mishra *et al.*, 2007; Hamacher *et al.*, 2007) have also shown that chemical inhibitors of CK2 are effective in inducing cell death, and that induction of death by chemical agents is blocked by forced overexpression of CK2 (Wang *et al.*, 2006a). Delivery of antisense CK2α into a xenograft prostate cancer in the mouse also demonstrated potent induction of apoptosis associated with significant reduction of the CK2 signal in the nuclear matrix (Slaton *et al.*, 2004). Of note, analogous to results on the relation of nuclear CK2 to apoptotic signals are the observations that nuclear matrix-associated CK2 demonstrates discrete cell cycle related changes that are not apparent in the cytoplasmic compartment (Wang *et al.*, 2003). Together, our studies indicate that a compartment of CK2 in the nucleus plays a key role in regulation of cell survival and death. The induction of apoptosis *in vivo* by intratumoral administration of antisense CK2 (Slaton *et al.*, 2004), or a peptide that impairs phosphorylation by CK2 (Perea *et al.*, 2004), has provided the proof of principle evidence for potential targeting of CK2 to produce cell death *in vivo.* Subsequently, we also originally reported that CK2 can be targeted by antisense CK2 delivered *via* the systemic route into the animal such that apoptotic response in tumor xenograft cells was observed *in vivo* (Ahmad *et al.*, 2005). These observations have paved the way towards devising potential approaches to cancer therapy by targeting CK2 (Unger *et al.*, 2004; Ahmad *et al.*, 2005). It is noteworthy that chemopreventive dietary agents such as resveratrol and EGCG (epigallocatechin-3-gallate) which are known to have mild apoptotic activity in cancer cells appear to mediate this effect at least in part *via* targeting of CK2, raising the possibility of employing these polyphenolic compounds alongside sub-optimal levels of inhibitors of CK2 in combination chemotherapy (Ahmad *et al.*, 2007). In the

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same context, it is noteworthy that multidrug resistance phenotype of CEM cells which are characterized by high CK2 level undergo reversion upon pharmacological inhibition of CK2 (Di Maira *et al.*, 2007). Although concern persists regarding the potential of targeting CK2 for cancer therapy because of its ubiquitous nature, the aforementioned observations suggest an emerging interest in this signal as a therapeutic target. We are currently investigating an approach to circumvent the host toxicity issues by delivering the CK2 targeting agent encapsulated in a nanocapsule for delivery specifically to cancer cells in vivo (Unger *et al.*, 2004; Ahmad *et al.*, 2005; Wang *et al.*, 2005b).

## Downstream Targets of CK2 in the Apoptotic Machinery

Mounting evidence suggests that there may be multiple nuclear and cytoplasmic targets that impact on the apoptotic machinery in response to modulations in CK2. For example, caspases 2, 3, 8, and 9 respond to alteration in the CK2 signal in diverse manners (Shin *et al.*, 2005; Wang *et al.*, 2006a). Procaspase-2 was shown to be a target of CK2 such that its dephosphorylation results in its dimerization and activation (Shin *et al.*, 2005). ARC, a protein that inhibits caspase-8 activity when phosphorylated, has also been identified as a CK2 target (Li *et al.*, 2002). The hallmark of nuclear apoptotic activity indicated by lamin A cleavage is strongly elicited by downregulation of CK2 and prevented by its forced overexpression (Ahmad *et al.*, 2006; Wang *et al.*, 2006a). Among the Bcl-2 family, Bid has been shown to be phosphorylated by CK2 (and also CK1) at serine residues in the vicinity of caspase-8 recognition site thereby preventing its cleavage by activated caspase-8 (Desagher *et al.*, 2001). In a preliminary observation, we noted that forced overexpression of CK2 in ALVA-41 prostate cancer cells caused an upregulation of Bid (Ahmed, *et al.*, unpublished results). Subsequent studies have shown Bid to be an interaction partner of the catalytic subunit CK2α (Olsen *et al.*, 2006). In our studies employing TRAIL as inducer of apoptosis in prostate cancer cells, we have found Bcl-xL and Bcl-2 proteins to be sensitive to CK2 status altered by treating cells with chemical inhibitors of CK2 (Wang *et al.*, 2006a). Inhibition or downregulation of CK2 results in loss of Bcl-xL and Bcl-2 proteins with Bax being upregulated, whereas overexpression of CK2 results in prevention of such changes in these proteins (Wang *et al.*, 2006a). The engagement of the mitochondrial pathway is clearly indicated by the alterations in cytochrome *c* release upon downregulation of CK2 while it is blocked by overexpression of CK2 (Wang *et al.*, 2006a). These various studies suggest that mitochondrial pathway plays a role in CK2 regulation of apoptotic activity and that certain of the Bcl-2 family of proteins in the apoptotic machinery are among the targets of CK2.

Attempts to identify proximal effectors of CK2 mediated modulation of apoptosis have revealed that intracellular $H_2O_2$ production upon downregulation of CK2 in prostate cancer cells may be an important signal for induction of apoptosis under these conditions (Ahmad *et al.*, 2006). These studies have shown that downregulation of CK2 by employing chemical inhibitors of CK2 or antisense CK2α or siRNA for CK2α to achieve downregulation of CK2 in prostate cancer cells (both androgen-sensitive ALVA-41 and –insensitive PC-3 cells) results in rapid increase in intracellular $H_2O_2$ which may be responsible for triggering the downstream pathways resulting in release of cytochrome *c*, activation of caspase-3, downregulation of IκB, translocation of NF-κB p65, and subsequent DNA fragmentation. These novel observations implicate a relationship between reactive oxygen species and CK2 such that inhibition of CK2 may result in elevation of intracellular $H_2O_2$ leading to activation of its downstream targets in the apoptotic machinery (Ahmad *et al.*, 2006). In this context, it is of interest to note that SAG (sensitive to apoptosis gene) protein which is upregulated on hypoxia induction undergoes degradation on phosphorylation by CK2 at Thr-10 (He *et al.*, 2007).

Another locus of CK2 mediated modulation of apoptotic activity appears to be the inhibitor of apoptosis proteins (IAPs). Among these, survivin has been shown to be influenced by the CK2

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status in cells (Tapia *et al.*, 2006). In accord with these observations, ongoing work in our laboratory has also shown that survivin expression cIAPs expression is reduced in prostate cancer cells upon downregulation of CK2; further, we have observed that cIAP1, cIAP2, and xIAP are also engaged downstream of the CK2 signal (Ahmed *et al.*, unpublished data).

Certain other genes that play a role in apoptosis are also affected by CK2. For example, in studies on TRAIL mediated induction of apoptosis, we observed downregulation of $cFLIP_L$ which was prevented by overexpression of CK2 in PC-3 prostate cancer cells (Wang *et al.*, 2006a); the significance of this observation may relate to the recent documentation that $cFLIP_L$ expression is necessary and sufficient to maintain resistance to TRAIL-induced apoptosis in prostate cancer cells (Zhang *et al.*, 2004). Upon phosphorylation by CK2, Max is rendered insensitive to cleavage by caspases (Krippner-Heidenreich *et al.*, 2001) while Myc is stabilized by CK2 mediated phosphorylation (Channavajhala and Seldin, 2002). In the NF-κB pathway, downregulation of CK2 by employing antisense CK2α resulted in nuclear translocation of NF-κB p65 (Ahmad *et al.*, 2006). Promotion of aberrant activation of nuclear factor-κB by CK2 in transformed phenotype of breast cancer cells has been documented (Romieu-Mourez *et al.*, 2002; Eddy *et al.*, 2005). Aberrant NF-κB activation by serum factors involving CK2 mediated activation of IKK2 has been reported in head and neck squamous carcinoma cells (Yu *et al.*, 2006). Likewise, CK2 has been found to phosphorylate the Fas-associated factor FAF1 in vivo and influence its translocation to the nucleus (Olsen *et al.*, 2003). A recent study has demonstrated that IGFBP-3 which is known to promote apoptosis in cancer cells is a substrate for CK2 mediated phosphorylation at ser-167, and that phosphorylation of this site by CK2 limits the ability of IGFBP-3 to induce apoptosis in prostate cancer cells (Cobb *et al.*, 2007). Analogous to these studies is the recent documentation that PML tumor suppressor which controls key pathways of growth suppression, induction of apoptosis and cellular senescence loses can undergo phosphorylation by CK2 at ser-517 which results in its ubiquitin-mediated degradation. These authors also found an inverse relation between CK2 and PML protein level in human lung cancer (Scaglioni *et al.*, 2006). PTEN, another important signal related to cell death and survival, appears to be stabilized on phosphorylation by CK2 (Vazquez *et al.*, 2001). In this context, it is interesting to note that AKT (a protein kinase with a role in cell survival) which requires phosphorylation at Ser-473 and Thr-308 by cognate kinases for its activation also has been found to harbor a CK2-specific phosphorylation site at Ser-129 that appears to contribute to its hyperactivation (Di Maira *et al.*, 2005). In a preliminary study, we also noted that forced overexpression of CK2 influenced AKT activation in ALVA-41 prostate cancer cells (Ahmed *et al.*, unpublished data). Further support for the interaction of CK2 and AKT has been provided in a recent report (Guerra, 2006).

## Concluding remarks

The brief overview of the functional activity of CK2 in the context of its ability to modulate cell death activity suggests that this signal has a broad ability to impact on diverse pathways engaged in the mediation of cell death. Fig. 1 depicts the dynamics of CK2 as involved in mediation of various functions in the cell under diverse conditions. As discussed above, a significance of these observations is that since CK2 downregulation by various means causes cell death, this approach has the potential of leading to novel strategies for cancer therapy. Studies in our laboratory are in progress along these line (Unger *et al.*, 2004;Slaton *et al.*, 2004;Ahmad *et al.*, 2005;Wang *et al.*, 2005b;Wang *et al.*, 2006b).

## Summary

Protein kinase CK2 is a ubiquitous and highly conserved protein serine/threonine kinase that is indispensable for cell survival. CK2 has long been implicated in cell growth and proliferation,

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and studies from several laboratories have suggested that CK2 plays a global role in affecting cell growth related activities. Recently, we documented that CK2, besides its role in cell growth and proliferation, can potently suppress apoptosis. Considering that CK2 has been found to be elevated in all the cancers that have been examined, the ability of CK2 to suppress apoptosis is particularly important in the context of cancer cell pathobiology since these cells exhibit dysregulation of both cell proliferation and cell death. Thus, overexpression of CK2 in cancer cells may impart a survival advantage by its action as a suppressor of apoptotic activity in these cells while promoting cell growth. In experimental studies, we have shown that overexpression of CK2 in cells can potently inhibit apoptosis mediated by a variety of agents including removal of survival factors, chemical and physical agents, and death receptor ligands. On the other hand, inhibition of CK2 by chemical inhibitors or by its molecular downregulation by antisense CK2 ODN or siRNA leads to potent induction of apoptosis. Downregulation of CK2 is associated with apoptosis mediated *via* effects on several downstream targets, and it appears that CK2 may have a global impact on the apoptotic machinery. While CK2 is present in both the nuclear and cytoplasmic compartments, several of its cell growth and cell death related activities appear to be associated with its signalling to the nuclear structures such as chromatin and nuclear matrix. In general, shuttling of CK2 to these compartments correlates with its role in cell growth and suppression of apoptotic activity whereas loss of CK2 from the nuclear structures is associated with induction of apoptosis and cessation of cell growth. These various observations on the biology of CK2 have led to our original proposal that CK2 is a potentially important target for cancer chemopreventive and therapeutic approaches; this is now being substantiated by recent studies.

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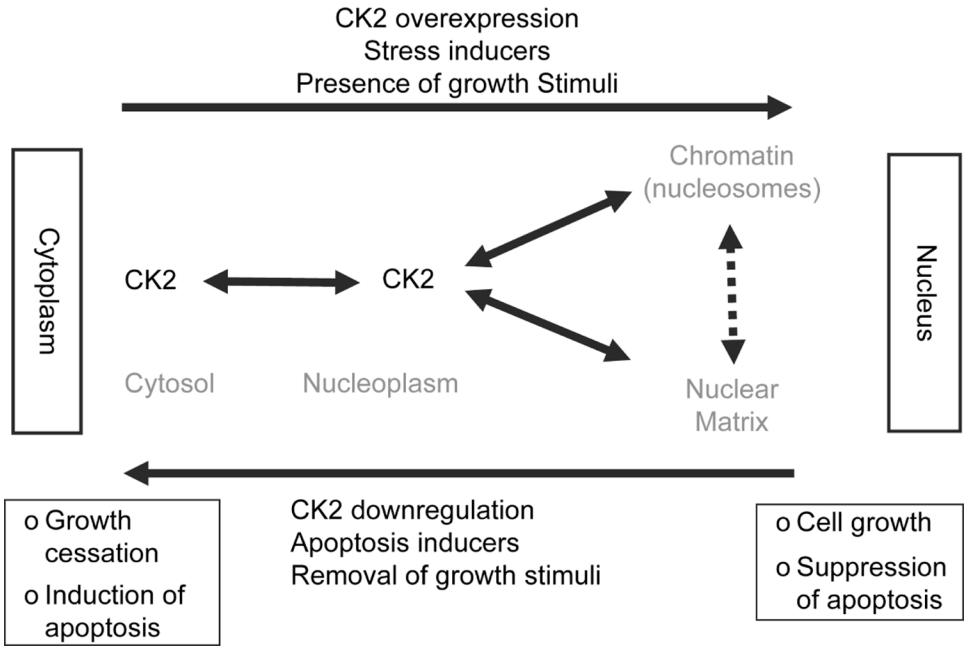


**Fig. 1.**
Cell response in relation to spatio-temporal dynamics of CK2 as affected by various stimuli.