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CK2: A key player in cancer biology

J. H. Trembley^{a,b}, G. Wang^{a,b}, G. Unger^c, J. Slaton^{d,e,f}, and K. Ahmed^{a,b,e,f}

K. Ahmed: ahmedk@umn.edu

^aCellular and Molecular Biochemistry Research Laboratory (151), Veterans Affairs Medical Center, Minneapolis, MN (USA), Fax: +6127252093

^bDepartment of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN (USA)

^cGeneSegues, Chaska, MN (USA)

^dUrology Service, Veterans Affairs Medical Center, Minneapolis, MN (USA)

^eDepartment of Urology, University of Minnesota, Minneapolis, MN (USA)

^fMasonic Cancer Center, University of Minnesota, Minneapolis, MN (USA)

Abstract

Elevated levels of protein kinase CK2 (formerly casein kinase 2 or II) have long been associated with increased cell growth and proliferation both in normal and cancer cells. The ability of CK2 to also act as a potent suppressor of apoptosis offers an important link to its involvement in cancer since deregulation of both cell proliferation and apoptosis are among the key features of cancer cell biology. Dysregulated CK2 may impact both of these processes in cancer cells. All cancers that have been examined show increased CK2 expression, which may also relate to prognosis. The extensive involvement of CK2 in cancer derives from its impact on diverse molecular pathways controlling cell proliferation and cell death. Downregulation of CK2 by various approaches results in induction of apoptosis in cultured cell and xenograft cancer models suggesting its potential as a therapeutic target.

Keywords

CK2; casein kinase 2; CKII; cancer; CK2 dysregulation; CK2 upregulation; prognostic marker; therapeutic target; nanoparticle; nanocapsule

Introduction

Investigations from several laboratories have resulted in detailed description of the characteristics of protein kinase CK2 as documented in a number of recent reviews [see e.g., 1–8]. CK2 is a ubiquitous serine/threonine protein kinase that is among the most highly conserved proteins in nature. Its heterotetrameric structure consists of two catalytic subunits

(~ 42 kDa α and 38 kDa α') and two regulatory subunits (~ 28 kDa β) in $\alpha_2\beta_2$, $\alpha\alpha'\beta_2$, or $\alpha'\beta_2$ configurations. The two catalytic subunits are linked through the β subunits, which are stimulatory rather than inhibitory to the kinase activity [9]. The β subunits may form a linkage with the nuclear matrix [10]. CK2 phosphorylates a large number of substrates, many of which are involved in gene expression and cell growth [2, 3, 5, 6, 11, 12]. Studies on the biological functions of CK2 have followed a circuitous route, and to further complicate the field, a considerable amount of earlier work did not use the name casein kinase 2 or CK2. For example, pioneering studies on phosphorylation of non-histone proteins in the nucleus in response to altered cell growth suggested the involvement of protein kinase activity towards these acidic proteins that later could be attributed to CK2 [see e.g., 12], and in fact many substrates of CK2 are nuclear-associated [e.g., 13]. An important feature of CK2 biology is the recognition that CK2 dynamically localizes to various cellular compartments under diverse conditions [14–16]. Indeed, nuclear structures such as chromatin and nuclear matrix acutely demonstrate modulations in CK2 in response to various growth and cell death stimuli [2, 4, 11, 12, 14–18]. As discussed subsequently, the nuclear matrix appears to be a key locus for CK2 signaling in the nucleus with regard to its function in cell proliferation and cell death. While CK2 is present in all cells (both normal and cancer), the focus of this review is to highlight its functionality in the cancer cell phenotype as compared with that in the normal, and to document aspects of CK2 function in cancer cell biology that promote consideration of this protein as a target for cancer therapy.

CK2 status in normal vs. cancer cells

Early studies of protein kinase signaling in the prostate [19] led to identification of CK2 as an important signal in the androgen- and growth factor-mediated regulation of growth in a normal cell growth model [20]. A key feature of CK2 regulation of cell growth and death relates to nuclear signaling, as evidenced by its shuttling to and from nuclear structures such as chromatin and the nuclear matrix in response to altered growth stimuli; these features of CK2 were originally documented by us [e.g., 2, 4, 11, 12, 14, 21–28]. Although the mechanisms involved in the *in vivo* regulation of CK2 are not fully understood, our work has suggested that CK2 targeting to specific loci in the cell represents an important aspect of its intracellular dynamics [e.g., 2, 14, 15, 17, 23, 29]. CK2 dynamics in the nuclear matrix appear to be the most remarkable indicator of cell signaling response leading to growth or death. Much evidence suggests that the nuclear matrix is intimately involved in cell growth, proliferation, and apoptosis [30–33]. For example, in androgen-responsive prostate cells, removal of survival signals causes loss of CK2 from the nuclear structures and is associated with inhibition of cell growth and induction of apoptosis. Restoration of the growth stimulus (androgen or growth factors) promotes survival and proliferation and is associated with an early shuttling of CK2 to the nucleus. Indeed, in the rat prostate model, loss of CK2 from the nuclear matrix at 24 h after androgen ablation is a marked 80%, with a concomitant 3-fold change in the number of cells in apoptosis. At 48 h, more than 92% of the CK2 is lost from the nuclear matrix with a concomitant 21-fold change in the number of apoptotic cells [14, 20, 25, 28]. That the nuclear matrix is the locale of several CK2 substrates further emphasizes the importance of these observations linking CK2 shuttling to and from the nuclear structures in response to various stimuli [2, 11, 12]. Recent studies have provided

further evidence that downregulation of CK2 expression promotes an early loss of CK2 from the nuclear matrix and is associated with induction of apoptosis in prostate tumor *in vivo* [34,35]. These observations suggest the potential involvement of a subcellular compartment of CK2 (i.e., that in the nuclear matrix) in the regulation of cell growth and apoptosis.

CK2 has been found to be upregulated in all cancers that have been examined. This increase in CK2, however, does not manifest itself at the level of message expression but rather at the level of protein, as determined in various studies by measurement of enzyme activity, immunohistochemistry or immunoblot analysis [see e.g., 3, 11]. However, it seems that elevated levels of CK2 alone are not indicative of dysregulation since high levels of CK2 are intrinsically present in certain organs such as brain and testes. CK2 in various cell types remains at a distinct and stable level under normal conditions. During cell proliferation, CK2 protein levels increase, then return subsequently to the original basal level characteristic of the particular cell type. As discussed later, stable levels of CK2 appear to be critical to homeostasis in the cell. Several features of CK2 status in cancer cells are noteworthy. First, tumor cells have a high nuclear concentration of CK2, whereas in normal cells, the protein is diffused in various compartments. Even more important, CK2 elevation in neoplasia reflects a complex state of dysplasia, not simply the proliferative state of the tumor cells [36]. Second, dysregulation of CK2 expression may relate to the severity of disease and even serve as a prognostic indicator [37, 38], an idea reinforced by recent observations in other laboratories [39, 40]. Third, as discussed subsequently, the recent discovery that CK2, besides being involved in cell growth and proliferation, is a potent suppressor of apoptosis supports its role in cell survival and firmly ties CK2 upregulation and function to the cancer cell phenotype [4, 11, 21, 41, 42].

Oncogenic potential of CK2

By itself, CK2 does not appear to be an oncogene. The proposal for the potential involvement of CK2 in oncogenesis has been based on observations that CK2 expression was upregulated in all cancers examined [e.g., 3, 8, 11]. Although it had long been appreciated that CK2 is elevated during normal and cancer cell proliferation, its role in the cancer cell phenotype remained unclear, leading to the assumption that elevated amounts of CK2 in cancer cells were simply a reflection of their proliferative status [3]. However, we originally demonstrated that increased CK2 expression in cancer cells reflected not only proliferation but also the state of dysplasia [36].

A significant aspect of CK2 biology is that it is essential for cell survival [e.g., 43, 44]. Accordingly, attempts to produce CK2 α and CK2 β -knockout mice have been unsuccessful (44,45). Moreover, modest downregulation of CK2 in the nuclear compartment (chromatin and matrix) leads to induction of widespread cell death by apoptosis [11, 12, 22, 34, 35]. In this context, it must be emphasized that cellular CK2 expression tends to be stable, and relatively small changes in the balance of CK2 expression have a large impact on cellular homeostasis. The apparent dysregulation of CK2 in various cancers suggests that at some stage in the process of transformation it undergoes significant change in its status, imparting an oncogenic potential to cells. Although CK2 by itself is not an oncogene, experimental animal studies have corroborated the remarkable contributory oncogenic potential imparted

by dysregulation of CK2. For example, overexpressed CK2 α in combined transgenic expression with *c-myc* or *Tal-1* resulted in a significant increase in the incidence of leukemia and lymphoma in mice [46–49]. Likewise, expression of CK2 α in mouse mammary gland under control of the MMTV-LTR resulted in a transgenic mouse model of breast cancer with several features resembling the human disease [48]. In each case, modest overexpression of the CK2 α transgene was sufficient to evoke enhanced oncogenic potential in the mice. These studies suggest that CK2 involvement in oncogenesis may be coupled to its modulation of the activity of other oncogenic signals in the cells. Noteworthy are the observations that CK2 can influence the stability of *c-myc* [49], and serve as a positive regulator of Wnt signaling in relation to tumorigenesis [50].

CK2: A key suppressor of apoptosis

Programmed cell death or apoptosis is a key component of cell physiology, and its dysregulation is recognized as a critical factor in oncogenesis. The latter aspect is especially pertinent to prostate cancer [41, 42, 51]. The initial observations that suggested a role for CK2 in the suppression of apoptosis were twofold. First, growth stimulus deprivation (androgen or growth factors) resulted in rapid loss of CK2 from the nuclear compartment (e.g., chromatin and matrix), which preceded the appearance of apoptosis [22]. Second, chemical and physical agents that induce apoptosis (e.g., etoposide, diethylstilbestrol, heat shock) result in rapid shuttling of CK2 to the nuclear matrix in PC-3 and ALVA-41 cells as an initial protective response [21, 52]. Similar observations have been made with respect to CK2 response to radiation [53]. Proof of the protective role of nuclear CK2 was obtained when ectopic overexpression of CK2 α prior to treatment with apoptosis-inducing agents was found to protect these cells strongly from apoptosis [21]. The specificity of the protective effect resided in the α but not the β subunit [21]. Further investigation has demonstrated that death receptor-mediated apoptosis in ALVA-41 and PC-3 cells also is suppressed by prior overexpression of CK2 α [54,55]. Thus, our work has established that CK2 can afford protection against apoptosis mediated via different pathways (intrinsic and extrinsic). Recent studies of other cancer models have provided additional supportive data for the role of CK2 in receptor-mediated apoptosis [53, 56–58]. It is noteworthy that several components of the apoptosis machinery are candidate substrates for phosphorylation by CK2 [e.g., 17]. Other pertinent observations are that CK2 facilitates repair of DNA single-strand breaks [59] and is a key regulator of the tumor suppressor PML through ubiquitin mediated degradation on CK2 mediated phosphorylation [60]. Interestingly, the c-terminal truncated form of the tumor suppressor adenomatous polyposis coli (APC) protein, which is an early event in most colon adenomas and carcinomas [61], has been shown to associate with CK2 without affecting its activity, whereas the full-length APC protein interaction with CK2 results in reducing its activity thereby exerting a growth inhibitory effect [62]. Finally, IGFBP-3 has been found to be specifically phosphorylated by CK2, which influences its apoptotic activity, an observation that is particularly significant since the IGF axis is believed to play an important role in the pathogenesis of many cancers [63].

CK2 interaction with other signaling molecules

In the foregoing, we discussed characteristics of CK2 in normal versus cancer cells and how CK2 upregulation contributes to suppression of apoptosis and oncogenesis. Overall, the data would suggest that CK2 affects a variety of molecules involved in diverse processes and, in fact, impacts on a wide range of cellular biochemical activities. This is not surprising considering that a rather large number of potential CK2 substrates have been identified by various investigators, and many of these substrates are members of complex signaling networks. [for details see e.g., 8, 11, 13, 17, 18]. Since CK2 is a ubiquitous enzyme present in both normal and cancer cells, it is possible that its activity towards a subset of substrates may depend on the state of oncogenesis, or that its activity towards certain substrates may have a more profound effect in supporting the biological activities of cancer cells. An elegant schematic account of potential links of CK2 to other pathways was given recently [8]. Here, we explore some of the signaling targets of CK2 pertaining to cancer.

Importantly, it appears that CK2 has a global role in transcription-related chromatin remodeling [27, 64, 65]. CK2 interactions and activity are intertwined with RNA polymerase I, II and III protein complex functions in general, and are specifically associated with various pre-mRNA transcription and splicing factors [66–73]. CK2 phosphorylation of numerous transcription and splicing factors likely changes their activity [see e.g., 11], and thus profoundly affects gene expression and proliferation. An effect of CK2 in androgen receptor-mediated transcriptional activity by androgen in prostate cells has been demonstrated [74], and it is conceivable that similar activity may take place in other cells in which steroid hormone receptors are involved. The role of CK2 in the regulation of Wnt signaling through phosphorylation of β -catenin in breast cancer has been well documented [48, 50]. Likewise, considerable evidence has been provided linking the function of CK2 in aberrant activation of NF κ B through activation of various IKK in breast cancer models [75–79]. CK2 phosphorylation of the splicing factor RNPS1 increases both the splicing and translation of a reporter pre-mRNA [67]. Molecules such as PTEN and Akt play important roles in cancer [e.g., 80, 81]. PTEN is phosphorylated by CK2, which influences its stability (82–85). Interestingly, Akt is activated by phosphorylation at various sites by Akt kinases, and was demonstrated to undergo phosphorylation by CK2 at a specific site (Ser 129), which results in its hyperactivation [86]. CK2 plays an important role in the functions of the RNA-processing protein nucleophosmin (protein B23), most notably through an impact on its nuclear localization [87–90]. The involvement of p53 and MDM2 in cancer is also well known [91,92], and the role of CK2-mediated phosphorylation of these proteins has been investigated extensively [e.g., 47, 93–98].

CK2 also plays a global role in the regulation of apoptotic pathways, and several downstream targets in the apoptotic machinery are impacted by CK2 activity [17]. These include, e.g., Bid [99, 100], Bad [101], Max [102], Faf1 [103], Bcl2 and Bcl-xL [104, 105], caspase 2 [106], caspase-inhibiting protein ARC [107], and inhibitor of apoptosis proteins (IAPs), including survivin [104, 108]. These studies have shown that survivin activity is regulated by CK2 at the level of transcription. Investigation of cIAP1, cIAP2, XIAP, and survivin in prostate cancer cells demonstrated their differential distribution in the cytoplasmic and nuclear compartments and also their expression levels were responsive to

altered CK2. Interestingly, decreased IAP levels in response to the apoptosis-inducing agents TNF α and TRAIL was potentially blocked on forced overexpression of CK2 [104]. Of note are the observations that fibronectin protection of TNF α -induced apoptosis is via the AKT/survivin pathway [109].

How does CK2 function in cancer cells?

To examine the role of CK2 in cancer cells as compared with the normal, it may be appropriate to briefly mention some key distinguishing aspects of cancer cell biology. Cancer cells can commandeer diverse molecular pathways to maintain themselves, and several distinct features of cancer cells can be identified, as discussed in several thoughtful reviews [see e.g., 80, 81, 110]. A number of hallmarks of cancer cells have been described—deregulated growth (self-sufficiency of growth signals, and insensitivity to antigrowth signals), evading cell death (apoptosis), limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, and genome instability [80, 81]. These features are present to varying degrees in all cancers; however, it seems that the particularly pervasive characteristics of cancer cells are deregulated proliferation and deregulated apoptosis [110]. These considerations raise the question as to how CK2 functions link with these hallmark features of cancer? Here, we attempt to discuss these issues.

As stated earlier, CK2 has been found to be upregulated in all cancers examined [see e.g., 3, 11], and we propose that increased CK2 expression is a contributing and/or sustaining factor in the deregulated growth of cancer cells. While CK2 is also upregulated in normal cells during proliferation, it subsequently returns to basal levels characteristic of the particular cell type. On the other hand, cancer cells appear to acquire a ‘stable’ new elevated level of CK2 expression higher than the level in counterpart normal cells [36, 38, 39, 111]. Further, the upregulation of CK2 in cancer cells reflects not only proliferation but the pathological status of various cells in a given field [36]. Following an example of prostate cancer cells which demonstrate androgen sensitivity (such as LNCaP) and androgen independence (such as PC-3), it was apparent that CK2 was equally functional in these cases and did not depend on the nature of growth factor requirement by the cells [20]. Finally, elevated levels of CK2 could contribute to oncogenicity in a given cell type by combining with another oncogene, as has been well illustrated in several aforementioned studies along these lines [45–49].

The second important feature of cancer is deregulated apoptotic activity. It appears that in some cancers the decrease in apoptotic activity is an even more important factor in cancer progression than increases in proliferation [e.g., 41, 42, 110]. As discussed above, CK2 is a potent suppressor of apoptosis [17, 21, 22]. Upregulation of CK2 can impact both the intrinsic and extrinsic apoptotic pathways mediated by diverse signals [8, 17]. Therefore, increased CK2 expression represents a mechanism by which cancer cells suppress normal apoptotic activity and cellular response to apoptosis-inducing agents.

Sustained angiogenesis is another important acquired capability of cancer [80, 81]. Clearly, the ability of cancers to generate an appropriate blood supply network in the tumor is critical to its survival. While the function of CK2 in the process of angiogenesis has not been extensively investigated, there are indications that it plays a role in this process. For

example, in experimental models of angiogenesis and retinal neovascularization, it was demonstrated that CK2 was involved in these processes. The data further suggested that inhibition of CK2 caused a suppression of angiogenesis and hematopoietic stem cell recruitment to retinal neovascularization sites [112–114]. We have also observed that when CK2 was downregulated by systemic administration of antisense CK2 α ODN to mice bearing a xenograft model of human prostate cancer, there was a marked reduction in microvasculature as indicated by the endothelial marker Cd31/Pecam-1 [35]. Of further note are the observations that CK2 may play a role in the regulation of HIF-1 activity, a hypoxia-responsive factor involved in tumor angiogenesis [115]. Together, these observations hint that CK2 may be an important player in the maintenance of angiogenesis in the tumor microenvironment.

With respect to the question of a role for CK2 in tissue invasion and metastasis, at present there are no systematic studies on this subject. Based on observations that CK2 may serve as a prognostic marker [37–40, 111], it may be surmised that cancer that exhibits a higher level of CK2 dysregulation is likely to be more aggressive and hence invasive. It is conceivable also that CK2 influences cancer cell invasion and metastasis by affecting the activity of molecules that are known to play a role in these processes. For example, green tea polyphenol epigallocatechin-3-gallate (EGCG) induced estrogen receptor α expression, reversing the invasive phenotype of breast cancer through activation of FOXO3a. Further, EGCG was found to inhibit the invasive phenotype of mouse mammary tumor cells driven by nuclear factor- κ B, c-Rel and protein kinase CK2 [116]. Similarly, mice transgenic for MMTV-c-Rel and CK2 α produce mammary tumors and cell lines which demonstrate a highly invasive phenotype [78]. It may be noted that EGCG and resveratrol caused a moderate inhibition of CK2 in prostate cancer cells, and this may also represent a mode of their activity as chemopreventive agents [117]. CK2-mediated phosphorylation of E-cadherin appears to influence its interaction with beta-catenin [118]. CK2 appears to also regulate adherens junction dynamics. For example, it was observed that disruption of adherens junctions is associated with a decrease in E-cadherin phosphorylation by CK2 [119]. Profiling of protein kinases in transformation of human ovarian epithelium in cell culture models has identified various kinases including CK2 to be associated with phenotypic manifestations of cancer progression [120]. Likewise, a few observations relating to the effect on matrix metalloproteases may be noted. It has been documented that UVB irradiation of human dermal fibroblasts causes CK2 mediated upregulation of MMP-1 and MMP-3 translation, whereas their major tissue inhibitor of matrix metalloproteinase-1 is not affected by CK2 [121]. Moreover, a recent study on the invasion-promoting MT1-MMP, which is directly linked to tumorigenesis and metastasis transactivation, show that its expression is strongly correlated with that of several genes including CK2 α [122]. In studies of breast cancer, observations on HDAC2 phosphorylation by CK2 may be important for tumor progression [123]. To sum, while the data are limited, it would appear that CK2 may also significantly influence the processes of invasion and metastasis.

CK2: A potentially important target for cancer therapy

An eventual goal of the investigations on CK2 is to translate basic observations to utility in patients. Induction of apoptosis is an attractive approach that has gained much attention as a

cancer therapeutic. We illustrate the potentiality of this approach by using prostate cancer therapy as an example. Prostate cancer is initially androgen sensitive and responds to androgen ablation. However, after the initial remission, the disease relapses in a generally fatal form because of the emergence of an androgen-refractory phenotype whose growth depends on a variety of autocrine/paracrine factors [e.g., 124]. Although docetaxel-based chemotherapy can improve survival in this situation, most patients die from chemoresistant disease. A number of molecular therapeutic approaches that have employed various gene targets have been investigated, but challenges such as design of delivery vectors and the effectiveness of the target gene remain [see, e.g., 125–127]. The IAPs and survivin have been proposed as targets for cancer therapy [128, 129]. However, as discussed above, their activity is strongly influenced by CK2, and thus it is likely that strategies to affect these molecules may be hampered by CK2 which is upregulated in cancer cells. A number of attempts to target protein kinases also have been undertaken [e.g., 125, 130]. However, we are the first to have proposed that downregulation of CK2 may be a strategic approach to inducing apoptosis in cancer cells, and thus merits consideration as a target in prostate cancer cells that may lead to novel cancer therapies [22]. Indeed, as discussed below, a compelling case can be made in support of our hypothesis.

We believe that to eradicate all tumor cells, it is important to consider targeting gene(s) that are uniquely indispensable for cell survival, as otherwise, tumor cells will escape death by recruiting an alternate pathway. This might be the situation, for example, with investigations directed toward a target such as *Bcl-2* [127]. Molecular targeting of protein kinases to downregulate their activity has excellent potential as a therapeutic approach, and indeed has been attempted in a few cases [125, 127, 129]. Of note, the kinase targets in these reports were not critical for cell survival, which might limit their utility for clinical translation. This is not the case for CK2 because it is essential for cell survival. We initiated this work by employing antisense CK2 α ODN to downregulate CK2 in cell culture and xenograft models (22, 34). However, different types of therapeutic agents that cause molecular or chemical downregulation of CK2 may be considered for such approaches. The importance of CK2 as a potential target for cancer therapy is supported by several considerations. First, compared with several other protein kinases, CK2 appears to be profoundly responsive to modulations of mitogenic signals in prostate cells [2, 11, 12, 18, 28]. Second, dysregulated elevation of CK2 in cancer cells reflects the pathologic status of the tumor [2, 11, 36–40]. Third, CK2 downregulation impacts not only cell growth and proliferation but also apoptotic activity in cancer cells, making its targeting a two-edged sword [4, 11, 12, 17]. Fourth, CK2 is indispensable for cell survival, and there appear to be no redundant pathways to compensate for its downregulation [43, 44]. In the case of prostate cancer, downregulation of CK2 would target both the androgen-sensitive and -refractory cells, producing an equally effective response regardless of the prostate cancer cell phenotype *in vivo*. Support for these considerations is derived from other recent studies. For example, targeting CK2 phosphorylation sites has been employed as means of inducing cell death which is presumably mediated by blocking of phosphorylation of CK2 substrates in cancer cells [131]. Likewise, chemical inhibition of CK2 appears to be a potential approach to achieve a therapeutic effect in experimental models [132]. Induction of apoptosis in cancer cells upon downregulation of CK2 may also rely on production of intracellular H₂O₂ which is known

to have several downstream targets in the apoptotic machinery [133]. While the above views provide a strong rationale for considering CK2 as a target for cancer therapy, it is important to note that CK2 is a ubiquitous enzyme and hence a key consideration would be to employ strategies that would spare normal cells while targeting CK2 in cancer cells. Clearly, the ubiquitous and indispensable nature of CK2 would raise concerns about host toxicity if it were downregulated in normal cells. Specific molecular downregulation of the targeted signal in tumors should be a key goal, and to that end, we have developed a novel nanocapsule approach to deliver the CK2 targeting agent specifically to primary and metastatic tumors *in vivo*. The use of s50 (sub-50 nm) nanocapsules composed of tenfibgen (a subdomain of the endogenous human protein tenascin) to deliver the various therapeutic agents to tumors while sparing normal cells should be a key to utilizing CK2 as the target for therapy [35, 55]. Further, such a strategy has a strong potential of targeting tumor metastases. Figure 1 illustrates that the tenfibgen nanocapsule carrying a luciferase cargo specifically targets the prostate cancer *in vivo* while sparing normal cells. Thus, delivery of a therapeutic agent that would downregulate CK2 through this approach should have a strong potential of eradicating the tumor while sparing the normal tissues *in vivo*.

Concluding remarks

The above discussion highlights the significance of CK2 in cancer biology. While much work is needed to elaborate on CK2 functions in cancer, a considerable amount of information supports the notion that it is a key player in the pathogenesis of cancer. Further, CK2 is a remarkably nodal molecule with its consistent upregulation in cancer, impact on a large number of cellular processes, and its essential for survival nature. Thus, CK2 merits serious consideration as a highly significant therapeutic target [17, 18, 35, 55]. Finally, we wish to emphasize that this report is not a comprehensive review of CK2 in relation to cancer but rather a brief overview of aspects of this subject, and we acknowledge that some of the views expressed here are likely to be speculative as considerable additional studies are needed to continue to define molecular links of CK2 involvement in cancer.

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Figure 1.

Strategy for tumor cell-specific delivery of CK2-targeting agents through s50 tenfibgen nanocapsules. Orthotopic implantation of TrampC2 tumor cells (2×10^6) was carried out and the tumor was allowed to develop for 4 weeks. To image the tumor position by luciferase Xenogen method, mouse A was injected intraperitoneally with 12 μg of s50 nm tenfibgen nanocapsules bearing luciferase plasmid, and mouse B with s50 nm tenfibgen capsules bearing sugar (trehalose). After 7 days, the mice were injected intraperitoneally with 120 mg/kg of luciferin, and imaged after 15 min in a Xenogen system. Mouse B (treated with s50 nm tenfibgen nanocapsules bearing sugar) has a tumor, but no signal is apparent (see arrow). However, mouse A (treated with s50 nm tenfibgen nanocapsules bearing the luciferase plasmid) shows signal in the tumor and tumor cell-invaded seminal vesicles which were proximal to the tumor (the primary tumor was located behind the tubules).