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Cellular functions of Protein kinase CK2: a dynamic affair

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Abstract. Protein kinase CK2 targets a vast array of substrates located in a number of cellular compartments, making the challenge of discriminating among these substrates a daunting task. However, as a signaling protein, CK2 could be targeted to different cellular compartments in response to various stress stimuli such as heat shock, UV irradiation, hypoxia, DNA damage and viral infections. This review will be focused on the evidence that the dynamic association of CK2 subunits and the substrate-dependent subcellular targeting of the enzyme are a likely point of regulation in response to a variety of signaling events. We propose that in addition to enzymatic substrate recognition, regulated CK2 localization to specific compartments should help to provide the exquisite specificity required for robust signal transduction. (Part of a Multi-author Review)

Keywords. CK2, stress-induced localization, substrate recognition, subunit interaction, signal transduction.

Introduction

CK2 is a multifunctional and pleiotropic protein kinase that has crucial roles in cell differentiation, proliferation and survival [1, 2]. Mounting evidence indicates that the enzyme is a component of regulatory protein kinase networks that are involved in several aspects of transformation and cancer [3–9]. In addition, studies on the *Drosophila* clock genes provide strong evidence for the involvement of CK2 in the molecular clock machinery [8, 9]. Through pioneering work more than 30 years ago, Thornburg and Lindell first described CK2 as a multisubunit protein kinase that is generated by the association of two α and α′ subunits (38–42 kDa) with a dimer of a 27-kDa β-subunit [10]. Subsequently, the multimeric structure of CK2 purified from different sources was confirmed, and the α/α′-subunits were shown to contain the catalytic domain of the kinase, whereas the β-subunit was identified as a regulatory component [11].

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A protein kinase on the move

CK2 is a relatively sparse signaling enzyme expressed at low levels in all eukaryotic cells. In contrast to most members of the kinome family, CK2 is a constitutively active enzyme, and to date, a unifying model for its potential cellular regulation has not been described. Many regulatory and biosynthetic pathways take place partly in the nucleus and partly in the cytoplasm, leading to a substantial flux of macromolecules between these two compartments. As a signaling protein, CK2 is a promiscuous kinase which has many cellular functions associated with a wide repertoire of substrates located in a variety of cellular compartments (mainly nucleus, cytoplasm and plasma membranes). This feature raises the question how CK2 activity can discriminate among its many substrates. While an exhaustive identification of the CK2-targeted proteins remains to be completed, a number of prominent CK2 substrates are membrane or chromatin bound proteins. The targeting of signaling molecules such as protein kinases to different cellular compartments is a fundamental process in the regulation of their activity. This raises the possibility that a localization-based signaling model, combining signaling microdomains in CK2 substrates located in differ-

ent subcellular compartments, could be essential in generating signaling specificity. This review will be focused on the evidence that the dynamic association of the CK2 subunits and their substrate-dependent subcellular targeting are a likely point of CK2 regulation in response to a variety of signaling events.

Nuclear CK2 substrates

In proliferating cells, CK2 phosphorylates, and alters, the activity of a number of regulatory nuclear proteins. Amongst these, DNA topoisomerase II is a major target of CK2 *in vivo* [12–14]. DNA topoisomerase II is a mitotic protein required for chromatin condensention during prophase. Both CK2 and topoisomerase II are predominantly nuclear enzymes that are dispersed throughout the cell during mitosis [15, 16]. Immunoprecipitation of DNA topoisomerase II from yeast results in a preparation that contains CK2, suggesting that the two proteins may associate in the intact cells. Indeed, recombinant CK2 and topoisomerase II associate to form a stable complex *in vitro*. CK2α is unable to associate with topoisomerase II, and it was observed that the presence of the β subunit in the oligomeric CK2 is required for this interaction, indicating that the stable association is not governed by a simple enzyme-substrate interaction. In contrast, topoisomerase II can be efficiently phosphorylated by both the isolated CK2α catalytic subunit or the oligomeric CK2 [12]. The biological significance of the stable topoisomerase II-CK2 complex is still unclear, but CK2 is responsible for the mitotic phosphorylation of DNA topoisomerase II on Ser-1469, which creates a phosphoepitope which is observed during mitotic entry and recognized by the MPM-2 monoclonal antibody [14]. A recent study reported that during interphase, topoisomerase II is co-localized with both CK2 and PP2A (protein phosphatase 2A). During early mitosis, PP2A is translocated from the nucleus, while CK2 remains in the nucleus until pro-metaphase thus permitting the formation of the MPM-2 phosphoepitope [17].

Induction and activation of the p53 tumor suppressor protein occurs in response to a number of cellular stresses triggering growth arrest and /or apoptosis. The predominant mechanisms of regulation of p53 sequence-specific DNA binding involve phosphorylation at specific sites and interaction with cellular proteins. Early studies have demonstrated that CK2 and p53 associate both *in vitro* and in intact cells in a molecular complex allowing the efficient phosphorylation of the C-terminal domain of p53 (Ser-392). Formation of this complex requires the presence of the β subunit of the kinase [18]. Mapping of the interaction sites between p53 and CK2β showed that a region of p53 upstream of the CK2 phosphorylation site (aa 287–340) is critical for binding of p53 to CK2β [19]. Phosphorylation of p53 at Ser-392 is increased in response to UV irradiation, and the purification of a UV-activated p53 complex was shown to contain CK2 and the chromatin transcriptional elongation factor FACT [20]. The association of this chromatin associated factor changes the conformation of CK2 and increases its specificity for p53 [21, 22]. CK2-phosphorylated p53 has been observed in the basal cells of UV-irradiated human skin [23], and mutation of this CK2 site in a murine transgene increases UV-induced skin cancer formation [24].

One important signaling role of CK2 may be the regulation of RNA polymerase (pol) III transcription. In yeast as well as in mammals, the core pol III initiation machinery consists of three protein complexes: RNA pol III, TFIIIC and TFIIIB, which contains the TATA binding protein (TBP). The target of CK2 among the components of the pol III transcriptional machinery is the TBP subunit of TFIIIB [25]. In yeast, a TFIII-associated kinase was identified as enzymatically active CK2. A biochemical analysis revealed that the regulatory CK2β subunit binds to TBP and is absolutely required for high TBP-associated CK2 activity and pol III transcription in unstressed cells. Thus, pol III transcription is modulated by CK2β, whose presence in the complex is likely determined by its physical interaction with TBP. The crystal structure of human CK2β reveals an acidic domain (domain I) that may serve as docking site for interacting proteins [26]. This acidic region which is conserved in yeast represents an attractive interacting domain with highly basic areas on the convex face of TBP [27]. Interestingly, transcriptional repression induced by DNA damage coincides with the down-regulation of CK2 activity due to dissociation of α/α′ catalytic subunits from the TBP-CK2 complex. Surprisingly, no change in TBP-associated CK2β was observed. In contrast, DNA damage signaling can trigger a dissociation of the TBP-associated CK2 holoenzyme which is correlated with the observed pol III transcriptional repression [28].

Histone deacetylases (HDACs) are enzymes that catalyze the removal of acetyl groups from lysine residues in histones and nonhistone proteins contributing to chromatin condensation. They play a pivotal role in transcriptional repression during cell cycle progression, cell proliferation and differentiation (for review, see [29, 30]). In humans and in mice, three classes of HDACs have been identified and many of them are regulated by post-translational modifications, particularly phosphorylation. Class I HDACs, such as $HDAC_1$ and $HDAC_2$, are components of large

multisubunit complexes. Both enzymes are phosphorylated in their C-terminal domain. However, unlike $HDAC_1$, which can be phosphorylated by several protein kinases including CK2, $HDAC_2$ is found associated with and phosphorylated uniquely by CK2. Interestingly, $HDAC_2$ phosphorylation promotes enzymatic activity but has no effect on transcriptional repression [31]. CK2 is upregulated in several cancers, and it was observed that CK2-phosphorylated $HDAC_2$ is preferentially associated with chromatin and the Sp1/ Sp3 transcription factors in human breast cancer cells [32]. Hypoxia and inflammation are both crucial factors in tumor progression. A recent study demonstrated that hypoxia is capable of enhancing $HDAC_1$ and $HDAC_2$ activity and that this activation coincides with CK2 stimulation in tumor cells. Interestingly, it was observed that upon hypoxic treatment, CK2β subunits were retained in the cytoplasm, whereas CK2α and CK2α' were shuttled to the nucleus where $HDAC_1$ and $HDAC_2$ are predominantly localized. In addition, knockdown of catalytic and regulatory subunits of CK2 revealed that HDAC are phosphorylated by CK2α and CK2α′ in the absence of CK2β [33]. Thus, these observations suggest that the catalytic activity of CK2 toward HDAC as a substrate does not require the heterotetrameric CK2 complex.

There is growing evidence that CK2 may be activated under hypoxic conditions. HIF-1 (hypoxia-inducible factor-1) is the main transcription factor involved in the adaptation to hypoxic conditions. It is composed of two members of the basic helix-loop-helix (bHLH) proteins: HIF-α and HIF-1β. Under normoxic conditions, HIF-α is rapidly degraded by the ubiquitin-proteasome pathway. In hypoxic cells, this degradation pathway is inhibited and HIF-α accumulates and migrates into the nucleus allowing the dimerisation with the HIF-1β subunit. This active complex then binds to HRE (hypoxia-responsive element) located in the promoter or enhancer of hypoxia-induced target genes involved in cell survival. HIF-1 is regulated through different mechanisms involving stabilization of the HIF-α subunit, regulation of the DNA-binding capacity and modulation of the transactivating activity. A direct effect of hypoxia on CK2 activity was recently reported, and this study provided the first evidence that CK2 plays a key role in regulating the activity of HIF-1 [34]. It was observed that under hypoxic conditions, CK2 activity is enhanced and activated CK2 positively regulates HIF-1 transcriptional activity without affecting HIF-α protein level. Of note, prolonged hypoxic stimuli (16 h) trigger the nuclear translocation of CK2α catalytic subunits into the nucleus, while the CK2β subunit is relocalized to the plasma membrane. While the mechanism of this regulation remains unclear, it was recently reported that p53 could be a necessary intermediate in the CK2-dependent regulation of HIF-1 activity [35]. Thus, CK2 is an important regulator of HIF-1 transcriptional activity.

Altogether, CK2 appears as a moving enzyme that could be rapidly recruited to target specific nuclear proteins in response to different stress stimuli. In addition, the dynamic properties of the molecular interaction between CK2 subunits is witnessed by the UV-induced dissociation of the CK2 subunits in *S. cerevisiae* and by the α/α′ subunit translocation in the absence of CK2β into the nucleus of hypoxic cells. This notion of independent movement of each CK2 subunit is consistent with live-cell fluorescence imaging studies that provided evidence of independent and rapid movement of CK2α and CK2β [36]. This difference in mobility was also evident at the level of their nuclear translocation: each CK2 subunit enters the nucleus as distinct subunits rather than a pre-assembled holoenzyme. Moreover, unlike CK2β, nuclear CK2α can be exported back to the cytoplasm through an exportin 1/ Crm1-dependent pathway. Therefore, CK2 subunits are not permanently associated with each other, but are able in response to various stresses to be targeted to specific partners and to participate in the transient formation of distinct macromolecular complexes.

Stress-induced CK2 mobilization

The notion that CK2 could be a key component of stress-induced pathways has been reinforced by several studies. As described above, in response to specific stress stimuli (heat shock, UV or ionizing radiation), a pool of the cellular CK2 relocalizes into the nuclear compartment. Each CK2 subunit was found associated with subnuclear domains such as speckles structures or nuclear matrix [37–39].

More recently, a novel role for CK2 in DNA damage repair was revealed. To maintain their genetic integrity, eukaryotic cells are equipped with sophisticated mechanisms to detect and repair DNA damage. XRCC1 is required for the rapid repair of chromosomal DNA single-strand breaks (SSBs) in mammalian cells [40]. At the molecular level, XRCC1 acts as a scaffold recruiting multiple components of SSB repair machinary. Loizou et al. were the first to show that in response to SSBs, CK2 phosphorylates XRCC1 and thereby enables its interaction with a putative fork head-associated (FHA) domain of polynucleotide kinase (PNK) [41, 42]. FHA domain is a ubiquitous phosphopeptide binding motif that can mediate interactions with phosphorylated proteins [42]. The assembly of the XRCC1-PNK protein complex re-

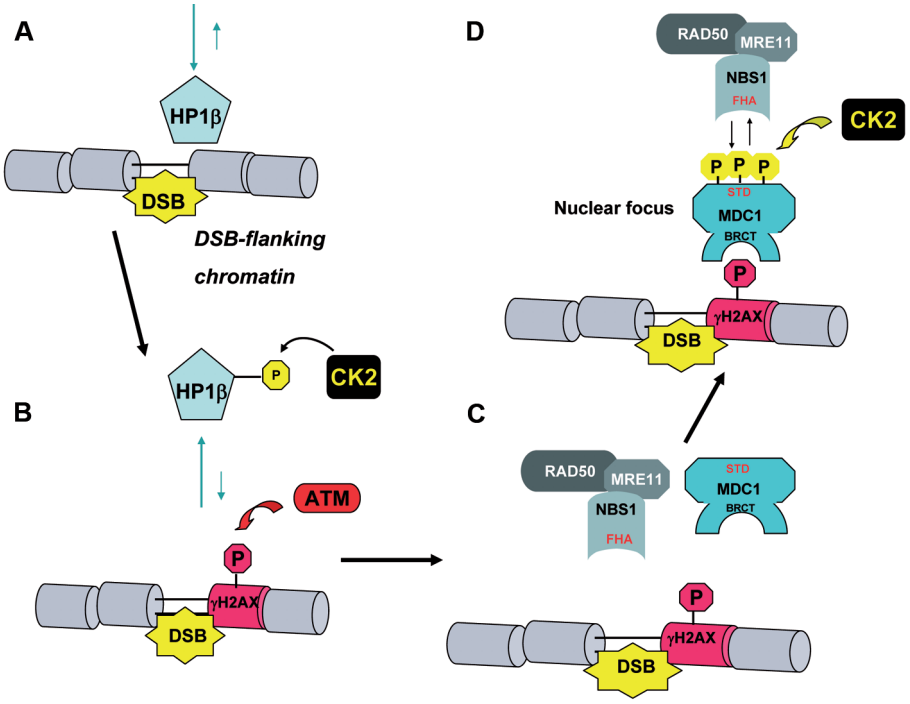

Figure 1. A hypothetical model of chromatin response to DNA double-strand breaks (DSBs) and the involvement of CK2 in this process. (*A*) In intact chromatin, the chromatin-binding protein HP1β interacts with methylated histone H3. (*B*) After DSB generation, CK2 phosphorylates HP1β on Thr51. This inhibits the binding of HP1β to methylated H3 and allows access of activated ATM to its target H2AX. (*C*) The accumulation of the MRN complex (Rad50, MRE11, NBS1) at the site of DSBs is not direct but requires the nuclear adaptor protein MDC1. (*D*) CK2 targets the STD repeats of MDC1, creating phosphoepitopes that are recognized by the NBS1-FHA domain, thereby stabilizing the interaction between MDC1 and NBS1. Formation of the MDC1-MRN complex is followed by its rapid accumulation at DSBs allowing the formation of nuclear foci and the recognition of phosphorylated H2AX (γH2AX) by the MDC-associated BRCT domains. Thus, CK2 plays an essential role to physically link the MRN complex via MDC1 to damaged chromatin.

quires the cluster of CK2 sites in XRCC1 and the FHA domain in PNK. Altogether, these data strongly suggest a novel role for CK2 in the recruitment/assembly of DNA repair protein complexes to sites of DNA strand breakage through an ability to interact with sites of poly (ADP-ribose) (PAR) synthesis at DNA strand breaks [41].

This unanticipated role of CK2 was recently extended to the pathways that deal with DNA double-strand breaks (DSBs). Cells react to DSBs by concentrating signaling and repair proteins in the vicinity of DNA lesions. Among the first cellular factors that accumulate at sites of DSBs is the MRE11-RAD50-Nijmegen breakage syndrome 1 (NBS1 [MRN]) complex. The most prominent NSB1 interaction partner is the ataxia telangiectasia mutated (ATM) kinase, the key enzyme phosphorylating histone H2AX. The NSB1 protein contains an FHA domain that is necessary for its retention at the DSB. However, the interaction at sites of DSBs between the FHA domain of NBS1 and phosphorylated H2AX (γ-H2AX) is not direct but is mediated by MDC1, a large adaptator protein that interacts with the MRN complex (for review see [43, 44]). MDC1 contains tandem BRCA1 C-terminal (BRCT) domains, which bind with specificity to phosphorylated γ-H2AX [45]. As a result, MDC1 is among the first proteins to accumulate at the DSB sites. Recently, four independent groups provided strong evidence that in reponse to DSBs, several acidic repeats, the Ser-Asp-Thr (STD) motifs present in the N-terminal part of MDC1, are phosphorylated by CK2 (Fig. 1). MRN was displaced from DSBs in cells containing mutant versions of MDC1 that lacked the CK2 phosphorylation sites. Therefore, these STD phosphorylations are functionally significant because they trigger productive interaction between MDC1 and the NBS1 FHA domain, thereby determining the retention of the MRN complex at sites of unrepaired DSBs [45–48]. From these studies a common theme emerges in which CK2 creates in response to SSBs and DSBs, phosphoepitopes on several scaffold proteins (XRCC1, XRCC4, MDC1) that serve as docking sites for FHA-containing signaling/repair proteins (PNK, NSB1).

One conceptual problem stems from the fact that the degree of compaction of chromatin is high, rendering the accessibility to various histone binding and/or DNA binding protein a difficult task. This is the case for the ATM kinase that should gain access to the H2AX, which may be buried deep within the compact

chromatin. A recent study by Ayoub et al. showed that, to facilitate the access of ATM to H2AX, the chromatin-binding protein HP1β must transiently dissociate from the chromosomal areas surrounding the DNA breaks [49]. It is known that HP1β binds chromatin via trimethylated lysine 9 of histone H3 (H3K9me). What is the mechanism underlying the increased intranuclear mobility of HP1β observed after DNA damage? The authors demonstrated that CK2 targets Thr51 in the chromodomain of HP1β, and this phosphorylation precludes binding of HP1β to H3K9me peptide *in vitro*. These results were validated in living cells by showing that phosphorylation of Thr51 was induced by DNA damage and that the chemical inhibition of CK2 or expression of a CK2 dominant-negative allele impaired this phosphorylation. Importantly, CK2 inhibition suppressed ATM-dependent H2AX phosphorylation. Together, these data suggest that one of the earliest chromatin-associated events in the vicinity of a DNA break includes CK2-mediated dissociation of HP1β or weakening of its affinity for H2AX (Fig. 1). It is known that DSB-induced chromatin response is a multistep process, requiring the local recruitment of remodeling enzymes with the capacity to change the chromatin topology. HP1β protein is dynamic and undergoes a continuous exchange. An acceleration of this exchange triggered by a damage-activated CK2 signaling cascade is likely. However, how CK2 can be activated locally within seconds at damage sites is not understood. Nevertheless, the physiological relevance of the CK2-HP1β suggests a possibly more general role of CK2 in rendering chromatin permissive for accumulation of repair and signaling proteins.

Membrane-associated CK2 substrates

Early immunocytochemical studies have shown that CK2 is mostly detected both in the cytoplasm and the nucleus of most cells. However, the enzyme has also been detected in highly purified plasma membrane preparations from rat liver and in SF9 insect cells expressing epitope-tagged CK2 subunits [50]. It was observed in this cell system as well as in rat liver plasma membrane that CK2β is the targeting subunit which mediates the tight association of the enzyme to plasma membrane components. Along this line, CK2 interacting protein-1 (CKIP-1) was shown to recruit CK2 at the plasma membrane [51]. The plekstrin homology domain of CKIP-1 is required for interaction with CK2. These results provide a possible mechanism whereby CK2 is targeted to plasma membrane and perhaps more importantly how it may be locally regulated. Indeed, there is increasing evidence that CK2 controls ion channel activity. A phospho-dependent regulation of the epithelial Na^+ channel (ENaC) was demonstrated in epithelia from airway and colon as well as in *Xenopus* oocytes expressing rat ENaC [52]. Phosphorylation by CK2 is essential for ENaC activation and stability. In *Xenopus* extracts, CK2 was translocated to the cell membrane where it binds to the expressed wt-ENaC but not to ENaC mutated on CK2 sites. The dynamic control of protein localization is an essential mechanism of specificity in signal-tranduction processes, particularly in neurons, where the diverse dendritic and axonal morphology provides a unique framework for the local regulation of signaling molecules. Voltage-gated Na^+(Na_v) channels are highly enriched at the axon initial segment (AIS) and nodes of Ranvier. A recent study provided clues to explain how neurons restrict Na_v channels to the AIS and nodes. The cytoskeletal scaffold ankyrin G (ankG), which has a conserved membrane-binding domain (MBD), is responsible for clustering Na_v channels. Bréchet et al. demonstrated that CK2-mediated phosphorylation of Na_v channels increased their affinity for the ankyrin MBD ~1000-fold. CK2 is highly enriched at the AIS of neurons, where it colocalizes with Na_v channels and ankG [53]. Thus CK2 appears to be spacially restricted to sites where it can promote the binding of Na_v channels to ankG. Action potential initiation depends on the density of Na_v channels; therefore modulation of channel number by regulating CK2 activity could be an important way to dynamically regulate the properties of the pike-generating machinery.

CK2 has also been described to influence other ion channels such as CFTR, the chloride channel that is defective in cystic fibrosis. A single amino acid, phenylalanine 508, located in the first nucleotide-binding domain (NBD1) of CFTR is often mutated (ΔF508) in cystic fibrosis CFTR. This mutation leads to reduced CFTR channel function due to defective intracellular transport and poor retention in the plasma membrane[54]. It has been reported that CK2 binds to and phosphorylates wt-CFTR. Both CK2 subunits were co-immunoprecipitated with CFTR under stringent conditions from normal epithelial membranes. This indicates that CK2 may be translocated by CFTR to the cell membrane as found for ENaC. Pharmacological inhibition of CK2 suggested that CK2 may regulate CFTR channel gating in intact cells. In a recent study, Pagano et al. demonstrated that both NBD1 wild-type and NBD1 ΔF508 are phosphorylated *in vitro* by CK2 at residues S422 and S670. Importantly, NBD1 was phosphorylated by CK2α but not by the holoenzyme. This observation prompted the authors to investigate further the links between CK2 and CFTR functionality. Intriguingly,

they found that peptides encompassing the 500–518 sequence of CFTR promote the phosphorylation of NBD1 by the holoenzyme in an F508-dependent manner while inhibiting its phosphorylation by the isolated CK2α. Of note, these peptides also perturb the interaction between the α and β subunits of CK2 [55]. Although the mechanism by which NBD1 interacts with CK2 is not fully understood, this rather complex CK2-CFTR association is the first described ΔF508-dependent CFTR-kinase interaction that provides a functional link in the most frequent form of cystic fibrosis.

Cell surface receptors are other examples of plasma membrane proteins that are regulated by CK2. The enzyme is a major lymphocyte kinase for the phosphorylation and activation of the CD45 protein-tyrosine phosphatase (PTP) in lymphocyte signaling [56]. The physical association between CK2 and a 19-aa acidic insert of CD45 cytoplasmic domain requires both CK2 subunits [57]. CD45 activity is essential for optimal activation of T and B lymphocytes in response to Ag stimulation [58]. It is suspected that CK2-dependent phosphorylation of this acidic insert that is located adjacent to the substrate-binding pocket of CD45 might alter its affinity and/or specificity for substrates. The transmembrane protein CD5 plays a key role in T lymphocyte signaling. In immature T cells, CD5 attenuates TCR/CD3-mediated signaling, whereas it provides costimulatory functions in mature T cells [59–61]. Following TCR activation in immature lymphocytes, CD5 is rapidly phosphorylated on tyrosyl residues by the tyrosine kinase $p56^{lck}$ (61). In contrast, it was demonstrated that in resting immature cells, CK2 is constitutively associated with the CD5 cytoplasmic domain and is activated by CD5 ligation [62]. The interaction of the CK2 holoenzyme with CD5 is mediated by the aminoterminus of CK2β. Cross-linking of CD5 leads to the sustain activation (10-fold) of CD5-associated CK2. The fact that this activation is independent of the net recruitment of CK2 to CD5 suggests that CD5 may function as a local regulator of CK2 activity. These studies were the first to expand the role of CK2 as a regulator of membrane proximal signals. This notion has important implications in autoimmune diseases because CD5 plays a direct role in the induction and progression of autoimmune encephalomyelitis (EAE). CD5-CK2 binding/activation-deficient mice were shown to be resistant to experimental EAE, providing a direct role for the CD5-CK2 pathway in neuroinflammatory disease [63].

The cell surface is directly involved in cell-cell interactions through receptors for extracellular signals. Several cell surface receptors, including cell adhesion proteins, are regulated through phosphorylation of their extracellular domains [64, 65]. Ecto-CK2-mediated phosphorylation of vitronectin, laminin-1 and collagen XVII has been reported [66–68]. CD98, originally discovered as a surface antigen in lymphocytes, has been found to be important for cell adhesion [69]. CD98 basolaterally expressed in intestinal epithelial cells is phosphorylated on its extracellular domain, by a T lymphocyte-associated ecto-CK2. Importantly, CK2-mediated phosphorylation of CD98 has functional relevance since it increases the binding of lymphocytes to intestinal epithelial cells [69]. Pro-inflammatory cytokines have been shown to upregulate CD98 expression in intestinal epithelial cells. Therefore, it is conceivable that, under pathological conditions, where extracellular ATP concentrations can reach high concentration, CD98 phosphorylation could have substantial effects on the binding affinity of CD98 for proteins expressed on the surface of lymphocytes, thereby aggravating intestinal inflammation.

Hijacking of CK2 by viral proteins

A multifunctional enzyme such as CK2 is logically exploited by infectious agents, and a role for CK2 in virally mediated pathologies is now clearly established. Different studies have revealed that several viral proteins can affect both the association and intracellular localization of CK2 subunits in infected cells. Upon adenovirus infection, it was observed that the CK2 subunits were redistributed to morphological distinct viral nuclear structures. Immunogold labeling revealed an association of CK2α with the nuclear bodies, whereas the CK2β subunits were found in the viral protein crystals [70]. These data suggest that the defense cell response to infection might involve a redistribution of the CK2 subunits.

Similarly, at early time after infection by the herpes virus type 1, CK2 is stimulated and interacts through CK2β with the immediate early protein IE63. Of note, CK2-mediated phosphorylation of IE63 correlates with a redistribution of CK2 from the nucleus to the cytoplasm [71,72].

The Epstein-Barr Virus early protein EB2, which is involved in the production of infectious virions, is also regulated by CK2. It was observed that CK2 subunits bind both individually and, more efficiently, as a complex to the EB2 N-terminus, whereas the CK2ß regulatory subunit interacts preferentially with the EB2 C-terminus [73]. CK2 phosphorylation of EB2 is critical for the efficient production of infectious virus by facilitating the nuclear export of early and late viral mRNAs.

During productive infection, the rodent parvovirus (PV) induces dramatic cytoskeletal alterations and physiological changes in fibroblasts leading to cell death and lysis. The viral NS1 protein has been identified as a major effector of PV cytotoxicity [74]. It has been reported that NS1 mediates CK2-dependent cytoskeletal alterations and cell death. Interestingly, NS1 can act as an adaptor molecule, linking the individual CK2α subunits to tropomyosin, modulating its substrate specificity and thus inducing degradation of tropomyosin filaments [75]. Consequently, NS1 has the ability to sequester CK2α and to target the kinase to tropomyosin and probably to other substrates, including regulators of cytoskeleton and components of signaling cascades. Collectively, these data indicate that several viral proteins are endowed with the capacity to exploit the dynamic properties of the individual CK2 subunits, selfishly hijacking them for their own purpose.

Functional consequences of CK2 dynamics

Clearly, the subcellular dynamics of the CK2 subunits are hallmarks of intracellular signaling molecules. The challenge for future studies is to dissect the spatial and temporal relevant mechanisms that control: 1) the association and dissociation of the CK2 holoenzyme; and 2) the distribution and diffusion dynamics of its subunits in response to various stress stimuli. It is important to consider that each CK2 subunit resides in a crowded environment with many potential binding partners. Temporal changes in the local concentration or in the relative affinities of the partners could be instrumental in dictating the segregation of individual CK2 subunits to different places. CK2β, in particular is a promiscuous protein interacting with a myriad of intracellular proteins, further implying that this subunit can exist independently of CK2α [76]. Indeed, localization and translocation are often mediated by modular proteins, and as such CK2β can generate multiple CK2-containing complexes. Many similar mechanisms for regulated localization of signaling proteins have been reported, and it can be argued that defining specificity based on localization may be more effective than specificity based on enzymatic substrate recognition. Thus, different CK2 subpopulations that can be distinguished on the basis of localization and (or) composition may be subjected to independent and local regulation in response to various stresses. This should encourage the development of different strategies to inhibit the interaction between the CK2 subunits. Albeit challenging, the ability to interfere with specific protein-protein interactions has already provided powerful means of influencing the functions of selected proteins within the cells. Structural properties of the holoenzyme showed that the CK2 subunit interface is relatively small, thus offering attractive opportunities for the identification of small molecules that modulate this interaction. In the CK2 holoenzyme structure, a segment located in the N-terminal region of CK2β forms a β-hairpin loop which inserts deep into a shallow hydrophobic groove present in the β4/β5 sheets of CK2α [77]. Site-directed mutagenesis and functional assays have revealed that only a small set of primary hydrophobic residues present in this segment of CK2β dominates affinity. Characterization of these hotspots led to the structure-based design of CK2β-derived cyclic peptides that are potent inhibitors of CK2 subunit interaction [78]. This study was the first step to set the framework for the discovery and development of chemical inhibitors of this interaction. The existence of a druggable pocket within the interface area of the CK2 holoenzyme was corrroborated by a recent structural study showing that one of the oldest albeit nonspecific CK2 inhibitors, D-ribofuranosylbenzimidazole (DRB), binds, in addition to the canonical ATP-cleft, to an allosteric site which was identified in the CK2α/CK2β interface. Inhibition kinetic studies demonstrated the dual-binding mode of this inhibitor [79]. In addition, screening of a library of podophyllotoxine indoloanalogues led to the identification of the first chemical inhibitors of this interaction [80]. These compounds were shown to block the interaction between the two CK2 subunits through direct binding to CK2α. Unexpectedly, these compounds trigger non-competitive inhibition of CK2α without interfering with the ATP-cleft. This inhibition was alleviated by CK2β, suggesting that this class of inhibitors binds to the CK2α/CK2β interface in/near the CK2β-binding pocket on CK2α. Structural insights from CK2α-inhibitor complexes would be essential to reveal the mode of CK2 inhibition by these compounds and may provide a platform for the structure-based design of a next generation of inhibitors. It is expected that these compounds will be substrate-selective, inhibiting the activity of the kinase against a subset of its substates. The targeting of signaling molecules to different cellular compartments in response to specific stimuli is a fundamental process in the regulation of their activity. Overall, the picture that emerges is that CK2 is a signaling molecule on the move, endowed with mobility and diffusion dynamics that are important parameters influencing its biological activity. In response to various stress stimuli, CK2 is prompt to change its distribution into distinct compartments. It is tempting to speculate that such reactivity contributes to the efficient transmission of signals initiated in different locations.

An open issue is the understanding of the molecular devices that allow various stress stimuli to mobilize and activate locally different pools of CK2. Spatial sequestration alone is not sufficient to explain these movements, and additional mechanisms such as interactions with substrates and/or binding partners or phosphorylation events might be effective in addressing the individual CK2 subunits or the holoenzyme to specific molecular complexes.

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