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Nuclear Matrix as an Anchor for Protein Kinase CK2 Nuclear Signalling

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Abstract Nuclear matrix (NM) is not only the structural basis for nuclear shape but also is intimately involved in nuclear functional activities. Among the modulatory factors that may affect these diverse activities are the signals that may influence the state or composition of the NM proteins. One such mechanism for altering the functional activity of at least some NM proteins may be the extent of their phosphorylation. Protein kinase CK2 appears to associate with NM and to phosphorylate a number of NM-associated proteins. Chromatin- and NM-associated CK2 is rapidly modulated by mitogenic signals. We propose that NM serves as a physiological anchor for nuclear signalling of protein kinase CK2 which may influence functions of NM such as transcription of active genes and growth.

Key words: nuclear matrix, phosphorylation, protein kinase CK2, chromatin, nuclear translocation, prostate, cell growth

In recent years, much evidence has been put forward that nuclear matrix (NM) provides the structural framework for chromatin organization. Indeed, NM is believed to impart the three-dimensional shape to the nucleus. NM also is the site of many growth-related activities, including DNA replication and control of gene activity in a cell- and tissue-specific manner. These aspects of NM studies have been the subject of a number of recent review articles [Berezny, 1991; Getzenberg et al., 1990; Nickerson et al., 1990; Stein et al., 1996].

Isolated NM comprises about 10% of the total nuclear protein and contains a small amount of DNA, variable amounts of RNA, and a minor quantity of lipid. The protein component forms the structural backbone of the matrix or scaffold. However, NM provides more than mere structural integrity, being intimately involved in many functional activities. In this regard, an important feature of the NM is that it is not a static entity but rather is a very dynamic structure. Intrinsic to the composition of the NM are a variety of structural and functional proteins [e.g., Berenzy, 1991]. Likewise, the inherent nature of the NM would dictate a transient binding of many other proteins to mediate their function, depending on the demands of the cell. The NM can thus serve as an anchor for certain enzymes which function at this locale, and their dynamic association and dissociation may represent a significant regulatory mechanism relating to the function not only of the enzyme in question but also of the activity of the NM.

Amongst the regulatory mechanisms involved in the functional activities of the cell is the post-translational modification of proteins *via* phosphorylation, which is controlled by the action of protein kinases (PKs) and phosphatases. It is therefore reasonable to consider that phosphorylation of NM-associated proteins is a key mechanism in controlling the functional activities of the NM [Getzenberg et al., 1990; Goueli and Ahmed, 1984; Ahmed and Tawfic, 1994]. This *Prospect* deals with the nature of the association of protein kinase CK2 (also known as casein kinase 2 or II) with NM and the potential significance of this association for NM functions. We propose that NM is a physiologically relevant anchor for CK2 signalling in the nucleus and that it is significantly involved in phosphorylation of a number of intrinsic proteins so as to modulate their activity.

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GENERAL CHARACTERISTICS OF PROTEIN KINASE CK2

Phosphorylation and dephosphorylation are significant regulatory mechanisms for a vast variety of cellular functions, including growth and proliferation. The state of phosphorylation, and thus the function, of cellular proteins is regulated by a complex network of PKs (and phosphatases), whose actions, in turn, are affected by numerous intracellular and extracellular signals such as hormones, growth factors, and mitogens [e.g., Edelman et al., 1987; Hunter and Karin, 1992; Meek and Street, 1992]. Certain PKs catalyze the phosphorylation of a specific amino acid in a particular protein substrate to mediate a distinct function. Other PKs are active toward a variety of putative substrates and thus participate in multiple functional activities. Among the latter group are the PKs commonly known as casein kinases, which belong to the messenger-independent protein serine/threonine kinase group. Of this group, CK2 has attracted much attention because of its possible multifunctional roles, including that in the control of growth and proliferation [Ahmed, 1994; Pinna, 1990; Tuazon and Traugh, 1991; Issinger, 1993; Litchfield and Lüscher, 1993]. CK2 is ubiquitous in eukaryotic cells and in general is active on acidic substrates. It is composed of three subunits α, α', and β (of M_r 42, 38, and 28 kDa), the primary structure existing as $\alpha\alpha'\beta_2$ or similar configurations, and localizes in both the cytoplasm and the nucleus. The regulatory subunit β is required for full activity of the catalytic subunit α. It can use ATP or GTP as phosphate donor, is potently inhibited by heparin, and is stimulated by the naturally occurring polyamines spermine and spermidine.

Chromatin and NM, which are central to the control of gene activity and cell growth, contain a variety of putative substrates for CK2 and thus appear to be among the critical loci of action of the enzyme [Ahmed et al., 1993; Tawfic and Ahmed, 1994a,b; Ahmed and Goueli, 1987]. Much work has implicated CK2 in the phosphorylation of a variety of cellular proteins involved in cell growth and proliferation, thus prompting the proposal that the enzyme plays a key role in these functions [e.g., Ahmed, 1994; Pinna, 1990; Tuazon and Traugh, 1991; Issinger, 1993; Litchfield and Lüscher, 1993]. Among the putative cellular substrates of CK2 are chromosomal proteins including nonhistones, nucleolar proteins, NM proteins, topoisomerases, RNA polymerases, steroid hormone receptors, SV40 T antigen, serum response factors, the products of certain oncogenes, heat shock proteins, $p34^{cdc}$, and the p53 protein [e.g., Meek and Street, 1992; Ahmed, 1994; Pinna, 1990; Tuazon and Traugh, 1991; Issinger, 1993; Litchfield and Lüscher, 1993]. In the case of topoisomerase II (an NM-associated enzyme), there is strong evidence that CK2-mediated phosphorylation enhances its activity [Cardenas and Gasser, 1993]. Likewise, the CK2 phosphorylation site in protein p53 plays a role in its DNA binding, and mutation of this site results in inactivation of the protein as a tumor suppressor [Meek and Street, 1992]. As will be discussed below, we have recently documented that CK2-mediated phosphorylation of the nucleolar and NM-associated proteins B23 and nucleolin (involved in ribosome and rRNA synthesis) is important in their stability [Tawfic et al., 1993a,b; 1995]. Recent work from several laboratories including our own has revealed that CK2 is among the most highly conserved proteins [e.g., Pinna, 1990; Tuazon and Traugh, 1991], a factor which suggests a fundamental function. Indeed, CK2 may be essential for cell viability [Padmanabha et al., 1990].

In our studies of the functional regulation of CK2 in relation to growth control, we have employed androgenic regulation of rat ventral prostate as an experimental model. In this model, androgen deprivation in the animal evokes a series of biochemical changes leading to apoptosis in 85% of the epithelial cells within 6 days; these changes are reversed, resulting in regrowth of the prostate, on administration of androgen to the castrated animals [e.g., Berges et al., 1993 and references therein). Androgens, like other steroid hormones, exert their actions *via* specific nuclear receptors by regulation of transcriptional activity [Coffey, 1988; Liao et al., 1989]. Thus, investigations of the regulation of CK2 in the prostate NM are of particular interest in regard to the androgenic control of prostatic growth.

ASSOCIATION OF PROTEIN KINASE CK2 WITH NUCLEAR MATRIX

Phosphorylation of NM proteins has been documented in several studies [e.g., Goueli and Ahmed, 1984; Tawfic and Ahmed, 1994a,b and references therein]. We observed that phosphorylation of prostatic NM proteins was profoundly

regulated by the androgenic status of the animal, and furthermore, the characteristics of the kinase reaction were suggestive of the involvement of CK2 in the phosphorylation of NM proteins [Goueli and Ahmed, 1984]. To address this point, we undertook a detailed examination of the isolated NM with respect to its ability to undergo autophosphorylation and the nature of the PKs involved [Tawfic and Ahmed, 1994a]. Our results showed that NM isolated from rat prostate or liver tissue is capable of catalyzing phosphorylation of the intrinsic proteins *in vitro*. The characteristics of this reaction indicated the involvement of CK2, as judged, for example, by the effects of several inhibitors of the kinase, its activity toward the specific synthetic substrate (Arg Arg Arg Glu Glu Glu Thr Glu Glu Glu), as well as detection of the immunoreactive protein by a polyclonal anti-CK2 antibody. The fact that CK2 is present in NM isolated from different tissues suggests that this association is a general phenomenon. According to our estimates of the CK2 in the isolated normal rat ventral prostate NM, the amount is about 40% of the nuclear-associated enzyme.

To determine whether the presence of CK2 in NM is physiologically relevant to the phosphorylation of NM proteins, we compared the phosphorylation profile of the NM proteins produced by NM-associated CK2 with that of NM proteins isolated after their phosphorylation had been mediated by PK activity intrinsic to intact nuclei or in intact cells. We found a remarkable similarity in the profiles in the three cases, suggesting that the phosphorylation of NM proteins catalyzed by CK2 is physiologically relevant. As discussed subsequently, CK2 intrinsic to the NM catalyzed phosphorylation of a number of the NM proteins, several of which could be identified in the gel electrophoretic profile as the putative physiological substrates for CK2 (e.g., topoisomerase II, protein B23) [Tawfic and Ahmed, 1994a].

NUCLEAR MATRIX AS SITE OF CK2 SIGNALLING

If NM-associated CK2 plays a signalling role in the nucleus, it would be expected to demonstrate rapid changes in its association with this structure in response to signals that alter the nuclear activity. To determine whether NM association of CK2 satisfied this requirement, we examined the amount and activity of CK2 in the NM isolated from rat ventral prostatic tissue from animals in various androgenic states [Tawfic and Ahmed, 1994b]. On androgen deprivation in the animal, there was a rapid and profound loss of NM-associated CK2, so that on orchiectomy, it was reduced by 75% and 90% within 24 and 48 h, respectively. This rate of decline is several times greater than that observed in the total nuclear-associated CK2 as well as in the chromatin-associated CK2 [Ahmed et al., 1993]. The rapid differential loss of CK2 activity in the NM was not owing to inactivation of the enzyme but rather to a decrease in the amount of CK2 protein present as confirmed by immunoblot quantitation.

To determine the nature of NM-associated CK2 changes in response to a growth stimulus, we followed the experimental design employed previously for our studies of chromatin association of CK2 [Ahmed et al., 1993]. In these experiments, rats castrated for a period of 5 days (when intrinsic nuclear-associated CK2 is about 10% of that of the normal controls) were given a *single* dose of 5α-dihydrotestosterone for a period of 1 or 4 h. The animals were then sacrificed, and NM from prostatic tissue was isolated, followed by determination of the amount and activity of NM-associated CK2. There was a rapid association of CK2 with the NM as a result of the androgenic growth stimulus, and the activity and amount of the enzyme increased in the NM fraction in a differential manner. Thus, at 1 h after the stimulus, the NM-associated CK2 had increased by 111% compared with a 45% increase in the total nuclei; whereas at 4 h, it was elevated by 229% and 112% in NM and total nuclei, respectively. This enhancement in NM-associated CK2 was even greater than that observed for chromatin under similar conditions [Ahmed et al., 1993; Tawfic and Ahmed, 1994b]. More recently, we have shown that EGF stimulation of a head and neck tumor cell line (C9–22) results in a rapid association of CK2 with the nucleus and NM [Faust, Gapany, Davis, Adams, Ahmed, unpublished data]. These results accord with the notion that CK2 is rapidly translocated to the nucleus in response to early mitogenic signals, as proposed previously [Ahmed et al., 1993; Lorenz et al., 1993]. In this context, it is noteworthy that despite the dissimilarities between the androgenic and growth factor signalling pathways, both of these disparate paradigms support a role for translocation of CK2 to the nucleus (and NM) as a mechanism of mitogenic signalling.

PHYSIOLOGICAL RELEVANCE OF PHOSPHORYLATION OF NM PROTEINS

The above-described modulations in NM-associated CK2 in response to androgenic growth signal are reflected in the phosphorylation of several of the intrinsic NM proteins [Tawfic and Ahmed, 1994b; Tawfic et al., 1995]. Thus, rapid loss of phosphorylation of prostatic NM proteins was observed on androgen withdrawal, whereas administration of androgen to castrated rats resulted in a concordant increase in phosphorylation of NM proteins. These early changes correlated primarily with the presence or absence of CK2 in the NM. Thus, it is likely that these phosphorylation events are of significance in regard to the functions of the NM. Although there are several putative substrates for CK2 in the NM, only a few of them have been examined in detail. Of particular note is topoisomerase II, which has been proposed to be a specific substrate for CK2, and it appears that its phosphorylation, catalyzed by CK2, stimulates its activity [Cardenas and Gasser, 1993]. We have examined protein B23 and nucleolin, which are among the substrates for CK2, in order to determine the functional significance of their phosphorylation.

Protein B23 is a nonribosomal phosphoprotein localized in the nucleolus and NM that has been implicated in ribosomal assembly and rRNA processing [e.g., Olson, 1990]. Because rRNA expression is among the earliest responses to androgenic stimulation of prostatic growth, we investigated the androgenic regulation of protein B23 and its phosphorylation in the prostate [Tawfic et al., 1993b; 1995]. Our results suggest that CK2 is the predominant kinase involved in phosphorylation of this protein. On androgen deprivation in the animal, prostatic protein B23 phosphorylation undergoes a rapid progressive decline. Quantitative immunoblot data of the corresponding amount of protein B23 present in the nucleus showed that at 24 h, there is a modest reduction in the amount of the protein but a significantly greater concurrent decrease in its phosphorylation. At 48 h post-orchiectomy, the amount of protein B23 is reduced by about 50%, whereas the phosphorylation is reduced by more than 90%. This differential loss of phosphorylation of protein B23 correlates with the decline in the NM-associated CK2 observed in prostate cells undergoing apoptosis in response to androgen deprivation [Tawfic and Ahmed, 1994b]. Prostatic protein B23 is degraded very rapidly after 48 h of androgen deprivation so that it is essentially undetectable at 72 h. This loss occurs despite the persistence of a significant amount of the corresponding mRNA—even at 7 days post-castration, when more than 85% of the epithelial cells have undergone apoptosis [Tawfic et al., 1993b]. Interestingly, under these conditions, the prostatic nuclei retain the ability to transcribe the B23 mRNA and this mRNA can be translated *in vitro*; the lack of new synthesis of protein B23 under these conditions is most likely attributable to the association of the majority of the message with free and short-stretch polysomes [Tawfic et al., 1995]. Further studies have shown that the downregulation of protein B23 in response to androgen deprivation for periods greater than 48 h relates to two coordinate signals: loss of CK2-mediated phosphorylation of the protein (secondary to loss of CK2 from the NM and the nucleus) and expression of a protease active toward the non-phosphorylated form of protein B23 [Tawfic et al., 1995]. It appears that CK2-mediated phosphorylation of protein B23 protects it from proteolytic degradation and thus may regulate its amount in the cell.

Nucleolin is another abundant phosphoprotein which has been implicated in various stages of ribosome and rRNA synthesis and localizes in the cell nucleolus and NM [e.g., Olson, 1990]. The characteristics of androgen sensitivity of phosphorylation and stability of prostatic nucleolin appear to be analogous to those observed for protein B23. The protein undergoes rapid degradation in concert with the loss of its phosphorylation (examined at 24 and 48 h after androgen deprivation). New protein and its phosphorylation by CK2 are observed within 6 h (the earliest time studied) after androgen administration [Tawfic et al., 1993a].

Taken together, these results underscore at least one aspect of the significance of CK2-mediated phosphorylation of NM-associated protein B23 and nucleolin; i.e., it protects them from proteolytic degradation.

POTENTIAL SIGNIFICANCE OF NUCLEAR MATRIX AS SITE OF CK2 SIGNALLING

Various considerations including the studies described above have prompted us to propose that NM serves as a physiological anchor for protein kinase CK2 signalling; our general concepts on the roles of NM-associated CK2 are

summarized in Figure 1. First, the association of CK2 with NM appears to be of high affinity. This is strongly indicated by the observation that a significant amount of CK2 remains associated with the NM, surviving the rigorous extraction procedures employed in the isolation of this fraction from the nucleus. We recently examined several procedures for the isolation of NM and observed the presence of the kinase in all the preparations [Tawfic, Davis, Faust, Gapany, Ahmed, unpublished observations]. Second, the amount of CK2 present in the isolated NM reflects the growth state of the cells, as evidenced by the observation that CK2 in the NM undergoes rapid changes in response to altered growth status. The changes in the levels of CK2 in the NM and chromatin precede the morphological or other biochemical changes associated with cell growth and cell death. Third, the NM-associated CK2 may exist in a dynamic relation with chromatin-associated CK2, possibly at the matrix attachment regions (MARs) analogous to the observed association of histone acetyltransferase with NM [Hendzel et al., 1994]. Preliminary data obtained in our laboratory suggest the existence of such an association of CK2 between chromatin and NM [Tawfic, Faust, Gapany, Ahmed, unpublished data], leading us to postulate that this kinase is located at the sites of active gene expression. Colocalization of CK2 and its various substrates within the NM may constitute a regulatory mechanism for different functions of NM. Fourth, a significant amount of CK2 appears to be present in NM when cell growth is at a steady state, suggesting its continued involvement in certain vital functions of the NM, as would be expected, for example, in the case of the prostate cells, where this basal level of activity is dependent on the continued presence of androgen. It is noteworthy that whereas NM protein represents only about 10% of the total nuclear protein, the amount of CK2 in the NM appears to be about 40% of that in the nucleus. In this regard, nuclear association of CK2 is different from the behavior of certain other kinases (e.g., CK1, PKA, PKC, and Ca/calmodulin-dependent PK), which do not appear to be localized in a significant amount in the nuclei isolated from normal rat prostate [Goueli and Ahmed, 1991] but may be detected there under certain conditions [see e.g., Getzenberg et al., 1990].

Our proposal that NM serves as an anchoring site for CK2 signalling [Ahmed and Tawfic, 1994; Tawfic and Ahmed, 1994a,b] accords with the general notion that CK2 plays a role in regula-

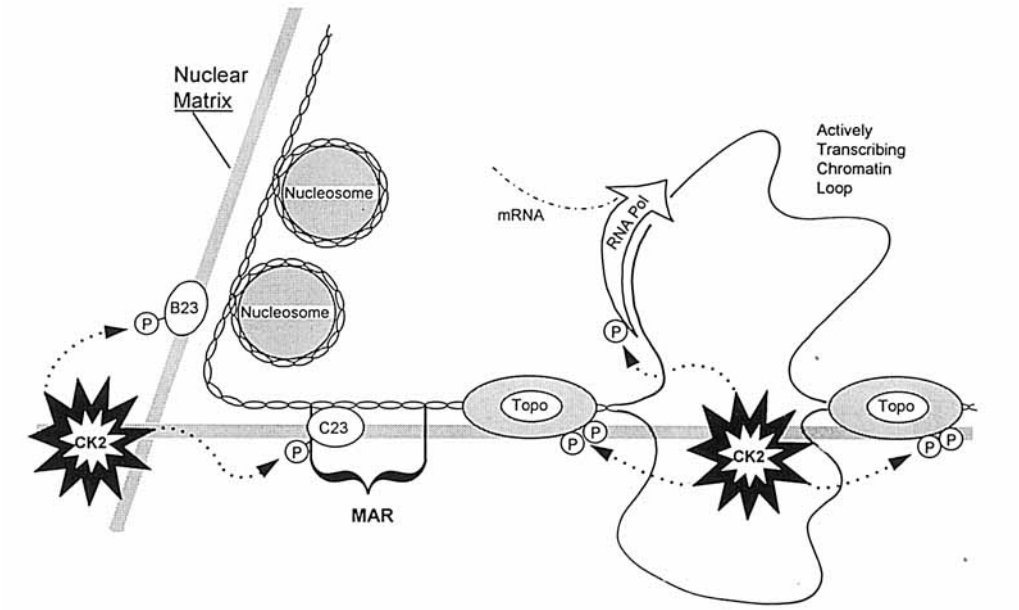

Fig. 1. Protein kinase CK2 signalling in nuclear matrix. A schematic representation of the involvement of protein kinase CK2 in the phosphorylation of some of the NM-associated proteins, such as protein B23, nucleolin (C23), and topoisomerase II (Topo). The possible physiological implications of their phosphorylation are discussed in the text. The physiological function of CK2-mediated phosphorylation of RNA polymerases I and II (RNA Pol) and several other NM-associated putative substrates of CK2 is unknown. The matrix attachment region (MAR) represents the site of active replication and gene expression.

tion of nuclear events, as exemplified by observations that CK2-mediated phosphorylation of certain oncoproteins (e.g., *Myb, Max, Myc,* c-*Jun*) regulates their functional activities [Litchfield and Lüscher, 1993; Bousset et al., 1994]. These considerations are of particular interest because a number of oncoproteins are known to be associated with the NM [Getzenberg et al., 1990].

Likewise, several lines of evidence suggest a role for CK2 in cell-cycle progression [Ahmed and Tawfic, 1994; Litchfield and Luscher, 1993; Tawfic and Ahmed, 1994b; Lorenz et al., 1994; Russo et al., 1992]. Considering that NM is intimately involved in DNA synthetic activity [Berenzy, 1991; Getzenberg et al., 1990; Nickerson et al., 1990; Stein et al., 1996], it would seem reasonable that association of CK2 with this structure would provide a mechanism for its function.

Our observations on the dynamic loss of CK2 from prostate cells undergoing apoptosis on removal of the androgenic stimulus hint at an association of the loss of the kinase with the process of apoptosis [Tawfic and Ahmed, 1994b; Tawfic et al., 1995]. We would like to offer a few speculative suggestions on how the reduction in nuclear (chromatin and NM)-associated CK2 may contribute to these changes. Dissociation of CK2 from the NM network may have direct (if CK2 acts as a "transcription factor") as well as indirect (via altered phosphorylation of certain substrates intrinsic to the NM) effect. The latter could influence the tensional integrity and consequently the functional activities of NM. This may result from altered tension and frequency of vibration in the NM (and possibly tissue matrix network) as a result of the changes in the NM proteins [Ingber, 1993]. Additionally, reduced phosphorylation and catalytic activity of certain substrates (e.g., topoisomerase II, protein B23, nucleolin) could result in further alterations in the tensional integrity of the matrix. In turn, these events could contribute to the morphological changes (such as shrinkage of nuclei) that occur in apoptosis.

Several laboratories including our own have documented an increase in CK2 in the neoplastic state [e.g., Ahmed, 1994; Issinger, 1993; Yenice et al., 1994; Gapany et al., 1995]. We postulate that association of CK2 with the NM may represent a key mechanism for the altered nuclear function under these conditions. One of the hallmarks of cancerous transformation in the cell is the histological alteration and abnormality of the nuclear structure. Because the nuclear structure is defined by the NM the abnormalities of the nuclear structure characteristic of cancer cells may be directly related to the changes in the 'tensegrity' of the NM. We speculate that altered CK2 association in the NM influences the structural as well as the functional characteristics of the NM under these conditions. Thus, it is likely that association of CK2 with the NM exerts effects on a variety of cellular functions. Further studies are needed to define the mechanism of CK2-mediated changes in NM and its consequences on growth control and regulation of gene activity.

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