Molecular Pathways

Control of Tumorigenesis and Chemoresistance by the DEK Oncogene

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Abstract

Slight modifications of chromatin dynamics can translate into small- and large-scale changes in DNA replication and DNA repair. Similarly, promoter usage and accessibility are tightly dependent on chromatin architecture. Consequently, it is perhaps not surprising that factors controlling chromatin organization are frequently deregulated (directly or indirectly) in cancer cells. DEK is emerging as a novel class of DNA topology modulators that can be both targets and effectors of protumorigenic events. The locus containing DEK at chromosome 6p22.3 is amplified or reorganized in multiple cancer types. In addition, DEK can be subject to a variety of tumor-associated transcriptional and post-translational modifications. In turn, DEK can favor cell transformation, at least in part by inhibiting cell differentiation and premature senescence. More recently, DEK has also been linked to the resistance of malignant cells to apoptotic inducers. Interestingly, a fraction of DEK can also bind RNA and affect alternative splicing, further illustrating the pleiotropic roles that this protein may exert in cancer cells. Here we will summarize the current literature about the regulation and function(s) of DEK as a proto-oncogene. In addition, the translational relevance of DEK as a putative diagnostic marker and candidate for drug development will be discussed. *Clin Cancer Res; 16(11); 2932–8. ©2010 AACR.*

Background

DEK, a highly conserved nuclear factor and the only member of its protein class, is preferentially expressed in actively proliferating and malignant cells, where it can reach up to 4 to 6 million copies per nucleus (1). DEK was initially described as the target of a recurrent t(6;9) translocation in a subset of acute myeloid leukemia (AML) patients (2, 3). Subsequently, DEK has been shown to promote tumorigenesis in a variety of cancer cell types, at least in part by its ability to interfere with cell division or DNA repair, inhibit cell differentiation, senescence and apoptosis, and cooperate with transforming oncogenes (Leave as such).

The bulk of DEK is bound to chromatin (1, 4, 5), preferentially to euchromatic regions (6). However, DEK can also be found within the nuclear matrix (7), or in interchromatin granule clusters (8). The precise determinants that DEK recognizes in the DNA are still under investigation. Although DEK exhibits some sequence-specific DNA binding, it primarily seems to recognize structural features (cruciform and supercoiled DNA; ref. 9). Two main domains in DEK are responsible for its interaction with DNA (see Fig. 1; ref. 10). Residues 87 to 187 are homologous to the scaffold attachment factor-box (SAF-box) domain (11, 12) found in multiple nuclear proteins (13). A second domain comprises residues 270 to 350 in the carboxyl-terminal region of the DEK protein, which is also responsible for multimerization (10).

Although the best known protumorigenic features of DEK are related to DNA binding, a fraction of DEK (approximately 10%) is associated with RNA (1) and can modulate RNA processing. Thus, DEK can affect 3′ splice site discrimination by the splicing factor U2AF (14). In addition, DEK can interact with serine-arginine-rich (SR) proteins (15) and other factors involved in exon-exon junction complexes (16), although the functional relevance of these interactions in cancer still needs to be defined. Finally, DEK can also be secreted, particularly by dying cells, and lead to the generation of autoimmune antigens that might play a key role in juvenile rheumatoid arthritis and other inflammatory diseases (17, 18).

The impact of DEK on mRNA splicing and autoimmunity has been addressed by other reports (14, 17, 18). Here we will focus primarily on the regulation and pro-oncogenic roles of DEK that are dependent on its DNA-associated functions.

Molecular Mechanisms of DEK Regulation

DEK has been shown to be upregulated in AML (2, 19, 20); retinoblastoma (21–23); glioblastoma (24);

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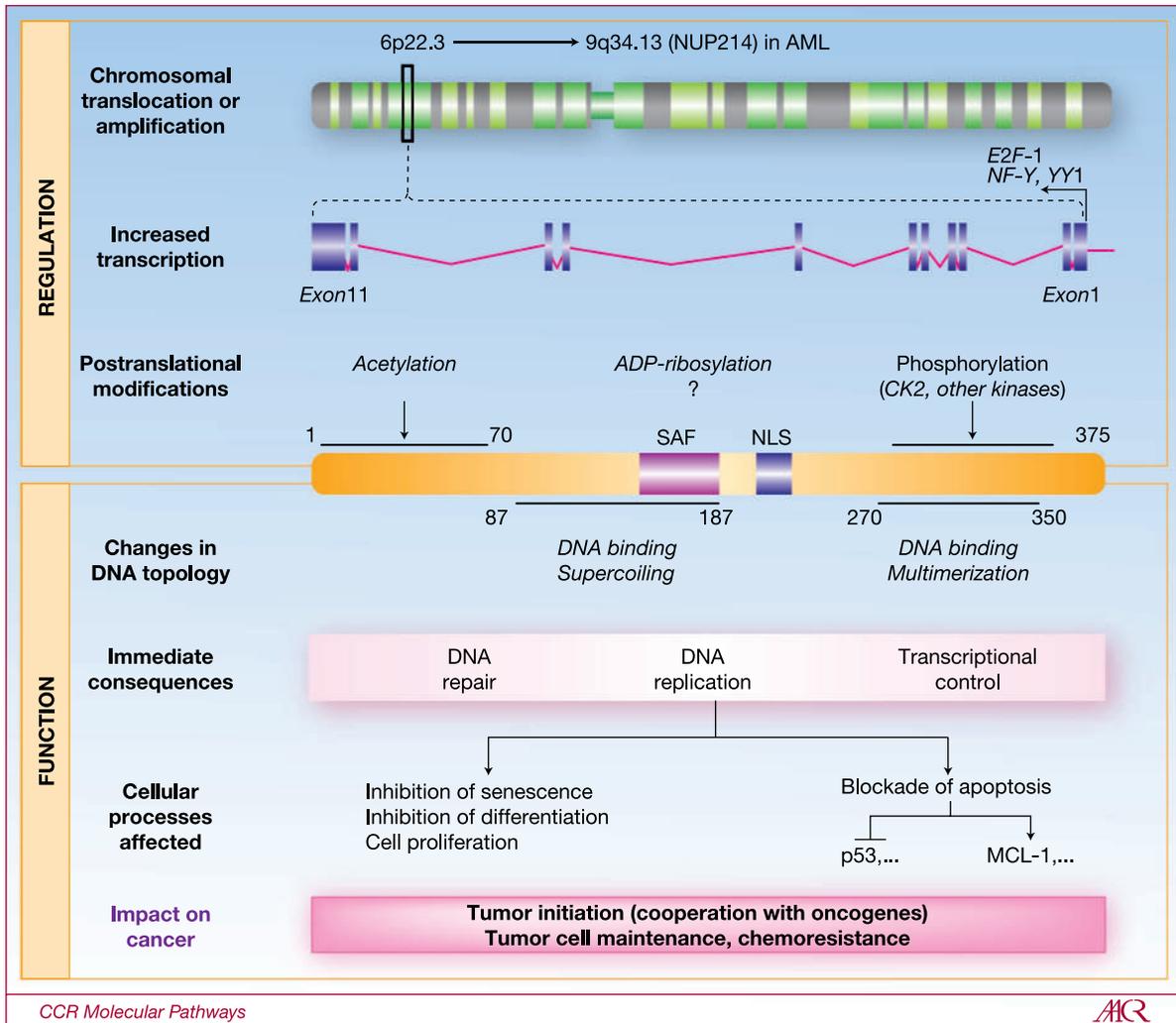*American Association for Cancer Research*

Fig. 1. Schematic summary of DEK regulation and function. DEK expression can be regulated at the DNA, RNA, and protein levels. Genomic translocations involving the 6p22.3 locus (where DEK maps) are frequent in a subset of AML. Amplifications and copy gains have been described in a variety of tumors, including retinoblastoma, bladder cancer, and melanoma. In addition, DEK mRNA transcription can be induced by various transcription factors (e.g., E2F-3, NF-Y, or YY1) whose expression and function are deregulated in multiple cancer cell types. In addition, acetylation, phosphorylation, and ADP-ribosylation can alter the affinity of DEK for chromatin and chromatin remodeling factors. By its ability to impinge on chromatin topology, DEK can influence DNA repair and DNA replication, as well as modulate the accessibility and occupancy of a still indeterminate number of promoters. Interestingly, although DEK is best known for its DNA binding features, it should be noted that DEK can also interact with RNA and components of the spliceosome. Ultimately, these functions favor tumor initiation, progression, and chemoresistance, at least in part by a concomitant blockade of senescence, differentiation, and apoptosis. By virtue of its protumorigenic roles and tumor cell–selective expression, DEK may represent a new class of drug targets and diagnostic markers.

hepatocellular carcinoma (25); melanoma (26, 27); and in an increasing list of other tumor types (20, 27–33). However, the mechanisms leading to this preferential accumulation of DEK in cancer cells are not completely understood. No mutations have been reported in the coding sequence of human *DEK*. However, a variety of other regulatory mechanisms have been identified at the DNA, RNA, and protein levels (see Fig. 1).

Genomic reorganizations-DNA amplification

As indicated above, *DEK* was discovered by the identification of the translocation t(6;9) (p23;q34) in a subset of

patients with AML, and was named on the basis of the initials of the patient DK (2). The observation that this chromosomal change was associated with an accelerated tumor onset and poor prognosis prompted a series of studies that ultimately support a causative role for DEK in tumor development. Specifically, the t(6;9) translocation was found to result in an in-frame fusion between nearly the entire DEK (missing just the last 25 amino acids), and two thirds of the nucleoporin NUP214 on chromosome 9 (Fig. 1). Although NUP214 (formally known as CAN) localized at the nuclear pore, the DEK-NUP214 fusion was found in the nucleoplasm (34).

Amplifications and copy gains at the short arm of chromosome 6, encompassing the DEK gene, were also found in the absence of translocations in a variety of malignancies, particularly in bladder cancer (29) and retinoblastoma (22, 23). Melanomas can also present with gains of the chromosome 6p area (35). However, other mechanisms of regulation of DEK may exist, as this protein can accumulate to high levels in AML, melanomas, and other tumors without specific amplifications or gains of the DEK locus.

Transcriptional regulation

Analyses aimed at identifying regulatory elements within the DEK promoter revealed binding sites for NF-Y and YY1 at positions 170 and 135, respectively, from the transcriptional starting site (36). NF-Y and YY1 are transcription factors with well-documented roles in cellular proliferation and transformation (37, 38), and thus could provide a mechanistic link between DEK upregulation and tumor development. Still, it remains unclear what the upstream modulators are that activate NF-Y and YY1 in order to signal through DEK in the context of malignancies.

Additional insights about the transcriptional control of DEK emerged from studies in virally induced pathologies. Analyses of human papillomavirus (HPV)-positive cervical cancer cells indicated that DEK can be transcriptionally activated by the E7 oncogene, a classical negative regulator of the retinoblastoma (Rb) protein (39). These results were confirmed by ectopic overexpression of E7 in primary human keratinocytes, and by the observation of DEK upregulation in human cervical cancer specimens infected with HPV (40, 41). Moreover, retinoblastoma and small cell lung cancers, both associated with Rb loss, present with high DEK levels (21). Consistent with Rb deficiency favoring transcription via the E2F family of proteins (42), chromatin immunoprecipitation assays showed that the *DEK* promoter is bound by endogenous E2F-1 in tumor cell lines (27). Mutation of E2F binding sites in the DEK promoter abrogated transcriptional activation in reporter assays (27). Therefore, tumor-associated E2F-1 activation may involve a concomitant activation of DEK mRNA transcription.

Post-transcriptional modifications

Post-transcriptional modifications add an additional layer of complexity in the regulation of DEK. For example, DEK can be phosphorylated, ADP-ribosylated, or acetylated. Phosphorylation has been reported to inhibit the binding of DEK to DNA, but favor the interaction of this protein with RNA splicing factors and potentially other nuclear proteins (14, 43). Similarly, poly(ADP)ribosylation and acetylation may reduce the affinity of DEK for DNA (44), but facilitate the interaction with other proteins involved in chromatin remodeling (see below).

With regard to phosphorylation, multiple consensus sites for casein kinase 2 (CK2) have been identified within the DEK carboxy terminus (43). In actively proliferating cells, DEK remains bound to DNA in a rather constant manner throughout the cell cycle. Yet, at the G1 phase there is a peak in DEK phosphorylation (43), but it is unclear to what extent this phosphorylation affects cell division. In line with this, DEK phosphorylation was recently suggested to act as a switch to favor or inhibit the association with proteins involved in chromatin remodeling or RNA splicing. Thus, in *Drosophila*, CK2-phosphorylated DEK can affect the deposition of histone H3.3, at least in the context of the nuclear ecdysone receptor (45). In overexpression studies, human DEK can also bind CK2 and act as a histone chaperone (45). Intriguingly, the fraction of phosphorylated, non-DNA-associated DEK, was found to accumulate in apoptotic cells (44). However, it is unclear whether this is the cause or consequence of cell death, and which kinases are involved, as CK2 may not be required in this process (44).

Another modification of DEK found to increase in cells dying in response to genotoxic agents is poly(ADP-ribosyl)ation (44). It has been proposed that this modification results from the interaction of DEK with poly(ADP-ribose) polymerase 1 (PARP1), likely to aid in DNA repair. Poly(ADP ribosylated) DEK is displaced from chromatin (46) and can be released into the extracellular space, where it can generate reactive auto-antibodies (44). This consequence of DEK modification may have important clinical implications as accumulation of DEK-auto-antibodies is found in synovial fluids of patients affected by juvenile rheumatoid arthritis or juvenile idiopathic arthritis (44). Therefore, deregulation of DEK's post-translational modifications may be critical to the pathogenesis of inflammatory diseases.

The affinity of DEK for DNA can also be reduced by acetylation (8). This modification localizes DEK to nuclear speckles or interchromatin granule clusters, which are well-known for containing RNA-processing and transcription factors (47). In contrast to phosphorylation that involves mostly the C-terminus of DEK, acetylation apparently affects lysines mapping within the first 70 amino acids (8). Together, these results support domain-specific modifications that may affect DEK conformation and/or interaction with distinct partners.

In addition to the above mentioned regulation of DEK by phosphorylation, acetylation, or ADP(ribosylation), it should be mentioned that DEK-DNA interactions can be modulated by a series of other chromatin-associated factors such as histone deacetylases, methyltransferases (SET), histone variants (H2A1.1), remodeling complexes (WSTF-SNF2h), or death modulators (Daxx; refs. 45, 46, 48–50).

In summary, DEK is a very dynamic protein, which may serve as a hub to recruit histones, histone modifiers and chromatin remodeling factors, and modulate their interaction with DNA. These activities of DEK depend on various post-transcriptional modifications, which in turn may respond to specific environmental or stress-related signals. In light of the hypothesis, it has been suggested that DEK could be one of the so-called "alarmins," molecules, that in the extracellular space, signal cell and tissue damage (44).

DEK in Tumor Progression and Drug Response

DEK-NUP214

From the initial discovery of the DEK-NUP214 fusion protein in a subset of patients with AML, DEK has been associated with tumor development. Yet, the precise mechanism of action of DEK-NUP214 in leukemogenesis has remained elusive. It has been recently reported that in malignant myeloid cells DEK-NUP214 expression correlates with a general activation of protein synthesis and increased the phosphorylation of eIF4E, a key factor in translational initiation and a marker for translational activity (51). In addition, in 293T cells, the DEK-NUP214 fusion protein was found to have an impaired ability to associate with histones and to be phosphorylated by CK2α and CK2β (51). If these results applied to the situation in human tumors, they would provide a molecular support for the hypothesis that the (refs. 6, 9) (p23;q34) translocation modifies the chromatin binding and remodeling activity of DEK.

DEK as a transcriptional modulator

Although it may be intuitive that the localization and function of DEK can be affected by its fusion to the nucleoporin NUP214 in AML, it is not clear how DEK exerts its protumorigenic effects in cancers that do not exhibit translocations of the 6p22-23 locus. It is plausible that the high levels of DEK found in these tumor types result in the occupancy of promoters and enhancers, which in normal cells remain "DEK-free." As indicated above, phosphorylation, acetylation, or ADP(ribosylation) can affect the affinity of DEK for DNA, and alter the stoichiometry of DNA-binding complexes. It is likely, although it has not yet been explored in sufficient mechanistic detail, that these post-translational DEK modifications are quantitatively and qualitatively different in benign and malignant tissues. Given the intricate and dynamic nature of chromatin, a comprehensive hierarchical map of these modifications, and how specifically they impact on DEK function and cellular fate, will undoubtedly pose a challenge. In fact, DEK can act as a transcriptional inducer or inhibitor, depending on the specific gene, cell type, and microenvironmental conditions. For example, DEK has been detected in transcriptional repressor complexes binding to Daxx in U937T cells (52); as well as to P/CAF, p300, or p65/nuclear factor-κB in HeLa cells (48, 53). On the other hand, other studies also in HeLa cells, indicate that DEK is largely excluded from heterochromatin and can accumulate at promoter-enhancer regions of select actively transcribed genes (54). Other activating effects of DEK have been linked to the activation of the transcription factor AP-2a (87MG or D17 astrocytoma cells; ref. 55) or the nuclear splicing factor U2AF (HeLa; ref. 14).

Inhibition of cellular senescence by DEK

In addition to assays aimed at uncovering DEK binding partners, assessing cellular and environmental cues that affect endogenous levels of DEK provided new insights on the multiple processes in which DEK is an active player. The first hint linking DEK to the proliferative status of cells was provided by the repression of its mRNA in two conditions: (i) HPV-positive cervical cancer cell lines undergoing senescence-like cell-cycle arrest, and (ii) primary keratinocytes and fibroblasts maintained for multiple passages in culture (and thus suffering telomere attrition). Interestingly, in both settings, DEK overexpression extended cellular life span, supporting critical roles for DEK as a senescence inhibitor (39).

As senescence bypass is an obligated hallmark of tumor cells, DEK activation may represent a new class of the so-called "tumor gatekeepers" (56). Proof for this hypothesis has recently been provided by selective depletion of DEK in melanoma cells by interfering short hairpin RNAs (shRNA). In a subset of metastatic melanoma cell lines, three independent DEK shRNAs prompted a progressive abrogation of cell proliferation, accompanied by the characteristic flattening, vacuolization, and acidic β-galactosidase activity of senescent cells (26). Considering the large number of genetic and epigenetic alterations that melanoma cells accumulate during their malignant transformation (57), it is remarkable that inhibiting the expression of a single gene can drive them out of the cell cycle. It also important to note that whereas human melanoma specimens show high DEK protein expression, their benign and senescent counterparts (nevi) are virtually negative (26).

Inhibition of differentiation and facilitation of cellular transformation by DEK

The interplay between DEK and the proliferative status of cells was also shown in the context of cellular differentiation. In human promyelocytic HL-60 cells or in human foreskin keratinocytes, differentiation led to DEK downregulation (41, 58). Moreover, mature cells from peripheral blood were found to contain a 10 fold lower amount of DEK than immature CD34-positive cells (59). Conversely, when DEK is overexpressed, differentiation programs can be counteracted, favoring oncogenic transformation. Thus, in the presence of ectopic DEK, immortalized keratinocytes could shift from differentiation to a hyperproliferative state when reconstituted into artificial epidermal rafts (41). Additionally, these DEK-expressing immortalized keratinocytes had an enhanced capability to grow in soft agar and form tumors in mice when transduced with the HRAS, and HPV E6 and E7 oncogenes (40). Further proof for an active protumorigenic role of DEK was recently provided by elegant studies in mouse models. DEK deficient mice were significantly more resistant than their wild-type littermates to the induction of skin papillomas in a classical 7,12-dimethyl-benz(a)anthracene (DMBA)-12-O-tetradecanoylphorbol-13-acetate (TPA) two-step carcinogenesis protocol (40). Whether DEK knockout mice are also protected from the development of metastatic tumors is an interesting question that warrants further analysis.

Apoptosis and chemosensitization by targeted depletion of DEK

Although overexpression studies have identified a role of DEK in favoring proliferation and blocking differentiation, targeted knockdown is unraveling key functions of DEK as a survival factor. DEK depletion in HeLa resulted in the induction of apoptosis, at least in part, as a consequence of the stabilization and activation of the tumor suppressor p53 (60), and the deregulation of multiple proteins with direct or indirect roles in cell viability (61). Nevertheless, the extent to which DEK controls cell survival is likely to depend on the genetic makeup of the tumor cells. For example, DEK depletion did not lead to an overt killing of melanoma cells (26). However, these cells still paid a toll in the absence of DEK. A subset of metastatic melanoma cells showed a progressive inhibition of cell-cycle progression upon DEK shRNA transduction, to ultimately stall into a senescence-like program (26). Other melanoma lines continued to proliferate, but became highly sensitive to genotoxic agents. Interestingly, this chemosensitization by DEK shRNAs was found independent on the functional status of p53. Instead, a new function of DEK was identified in the transcriptional control of the anti-apoptotic factor MCL-1 (26). MCL-1 upregulation is a general feature of aggressive cancers, which also express high DEK levels. Therefore, it is tempting to speculate that the MCL-1 locus may be under the control of DEK in multiple tumor types.

Clinical-Translational Advances

DEK as a tumor marker

Since its discovery as the target of the t(6;9) translocation in a subset of AML patients, DEK has been recurrently associated with tumor development. In fact, this translocation has been suggested to be considered in AML patient stratification (62). Chromosomal alterations at the *DEK* locus are now known not to be a universal feature of malignancy, even in AML (20). However, the increasing list of tumor types showing high DEK protein expression that can be easily detected by commercially available antibodies raises the exciting possibility of using DEK as a tumor marker. The finding that DEK expression levels can distinguish benign nevi from malignant melanomas (26) is a prime example of a clinically relevant setting in which this protein may prove to be highly useful. Moreover, as DEK may be present at higher levels in immature cells than in their differentiated counterparts (59), it could also aid in gauging the differentiation potential of tumor cells. Whether DEK can mark stem or tumor initiating cells is an interesting question that merits further analysis.

DEK as drug target

Being an abundant and pleiotropic factor that binds large stretches of chromatin, it could perhaps have been expected that interfering with DEK functions would result in intolerable side effects in normal cells. However, the fact that DEK-deficient mice are viable whereas DEK-depleted tumor cells enter into senescence or apoptosis (40), supports a DEK-dependent "oncogenic addiction" that could be exploited for drug design. From a translational point of view, it is also interesting that intratumoral injection of DEK shRNAs can lead in the induction of apoptotic features in mouse xenografts generated by Ras/E6/E7-transformed human keratinocytes (40). The feasibility and efficacy of sustained DEK downregulation has yet to be proven in physiologically relevant tumor models or clinical settings. However, the development of new strategies for small interfering RNA (siRNA) delivery, and the observation that normal cells may be less sensitive to DEK downregulation than their hyperproliferative counterparts (40), offers a window for therapeutic intervention. The fact that DEK controls the resistance of tumor cells to genotoxic agents (26, 44) could also be used as a guide for a rational selection of compounds that may better synergize with DEK-inhibitor agents. A proof of principle for this hypothesis has been recently suggested in experimental models of melanoma (26). The observation that DEK is released from apoptotic cells and generates auto-antibodies may also provide an alternative to assess drug efficacy in pharmacokinetic or pharmacodynamic studies of pro-apoptotic agents.

The understanding of regulatory elements in the DEK promoter has additional translational implications. Specifically, the transcriptional control of DEK by E2F-1 (27) may be relevant in the context of drug response. Thus, anticancer agents that affect cell-cycle proliferation may downregulate E2F-1 and, consequently, DEK expression and the corresponding DEK-dependent functions.

In summary, the DEK oncogene is overexpressed in a broad spectrum of cancers and plays an active role in tumor initiation, maintenance, and drug response. There are still many open questions about the regulation and function of this protein, which will certainly keep researchers active in multiple disciplines. From a structural point of view, it is unclear how DEK can bind chromatin in a sequence unspecific manner but act at discrete sites in the RNA [in fact the RNA-interacting domain(s) of DEK are unknown]. Which of the reported post-transcriptional modifications that might determine this differential DNA versus RNA recognition are also not well understood. The histone and chromatin modifiers, as well as the components of the spliceosome that interact with and are affected by DEK, need also to be better defined. Importantly, a thorough genome-wide analysis is required to establish a hierarchical map of DEK-dependent modulators of cell proliferation and cell viability. The crosstalk between DEK, p53, Rb, and the apoptotic machinery also deserves attention, as this information may guide the development of improved therapies. Although these questions are being investigated, the available knowledge about the tumor-selective expression and function of DEK can already be funneled into clinical practice (in the form of diagnostic markers, and as a platform for drug design). These results illustrate how a multidisciplinary characterization of

chromatin organizing factor can efficiently merge basic and translational research in oncology.

Disclosure of Potential Conflicts of Interest

The authors declare no potential conflicts of interest.

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