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Nuclear Protein Isoforms: Implications for Cancer Diagnosis and Therapy

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ABSTRACT

Post-translational modifications (PTMs) of nuclear proteins play essential roles in the regulation of gene transcription and signal transduction pathways. Numerous studies have demonstrated a correlation between specific nuclear protein isoforms and cellular malignant process. This communication reviews the impact of major PTM events such as phosphorylation, acetylation, methylation, ubiquitination, and sumoylation on several important nuclear proteins including p53, histones, proliferating cellular nuclear antigen (PCNA), and retinoblastoma protein (Rb) in the process. In addition, the implications of the PTMs as cancer biomarkers and therapeutic targets are considered. J. Cell. Biochem. 112: 756–760, 2011.

KEY WORDS: NUCLEAR PROTEIN ISOFORMS; PHOSPHORYLATION; METHYLATION; ACETYLATION; UBIQUINTINATION; SUMOYLATION

Progress in identifying cancer-associated molecules and targeting these biomarkers has advanced clinical cancer diagnosis and therapeutics. Post-translational modifications (PTMs) of nuclear proteins are involved in activating and inactivating critical signaling pathways in cellular processes of malignant transformation and progression. The major PTMs of nuclear proteins that play significant roles in these processes are phosphorylation, acetylation, methylation, ubiquitination, and sumoylation.

Acetylation, a prominent PTM in mammalian cells, occurs on lysine residues of proteins and has been demonstrated to regulate cellular functions. A recent proteomics study found that approximately 1,800 proteins were modified by lysine acetylation [Choudhary et al., 2009]. These proteins have diverse functions ranging from the coordination of cell signaling, protein–protein and protein–DNA interactions, to protein stability and localization. Nuclear proteins involved in DNA damage repair, transcription regulation, and chromatin architecture are modified by acetylation and may be aberrantly regulated in cancer cells.

Protein phosphorylation generally takes place in cellular cytoplasm and leads to a cascade that activates proteins to translocate into the nucleus [Karin and Hunter, 1995]. Extracellular signals such as hormone and cytokine stimulation initiate signal transduction cascades that involve nuclear proteins like CREB and STAT. Dysfunction in these signal transduction events causes over-stimulation of a number of nuclear proteins and facilitates the process of cell transformation and tumor progression.

Methylation imbalances occur in cancer cells through the modification of DNA or proteins. Protein methylation has primarily been studied in the context of histones and regulation of chromatin structure. Methylation of histones is believed to facilitate increased transcription levels of proteins related to the malignant transformation of cells [Zheng et al., 2008].

Protein ubiquitination is catalyzed by a three-step enzymatic mechanism linking ubiquitin molecules to the targeted proteins and traditionally has been considered as an important pathway in protein degradation. Monoubiquitination that serves as a signaling mechanism, especially in DNA synthesis and repair, may potentially serve as novel chemotherapeutic targets. Sumoylation, a process by which a small ubiquitin-like modifier (SUMO) is conjugated to target proteins, is involved in a variety of molecular events including nuclear trafficking and gene expression. Although the linkage between sumoylation and tumorigenesis is poorly understood, studies have suggested sumoylation plays an important role in cancer development [Ande et al., 2009].

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p53

Inactivation of the p53 tumor suppressor is a key factor in a broad range of tumors. Over 50% of sporadic tumors harbor mutations in the p53 gene [Gu et al., 1997]. As a transcription factor p53 regulates the expression of genes involved in cell-cycle arrest, senescence, and apoptosis. Understanding functional consequences of the interplay of various PTMs on p53 has been an ongoing study.

Under normal conditions, the level of p53 is maintained at a very low level by the ubiquitination and degradation effect of MDM2 that acts as an ubiquitin ligase. MDM2 binds to p53 and covalently attaches ubiquitin to it for degradation. In response to stress, p53 undergoes several protein modifications such as phosphorylation and acetylation that help stabilize and activate p53 in regulating gene transcription. These PTMs cause conformational changes of p53 and mask ubiquitination sites on p53, disrupting the interaction between p53 and MDM2 and thereby inducing p53 function [Ito et al., 2001]. Phosphorylation also enables p53 to interact with transcriptional co-activators such as p300 and CBP that acetylate the C-terminus of p53 and expose its DNA-binding domains for specific gene activation or repression [Meek, 2009]. Additionally, acetylation alters the selective transcription of p53 target genes. It was found that acetylation of lysine 120 (K120) on p53 was essential for an apoptotic response, but not for growth arrest and that acetylation of any one of the sites at K164, K120, and the six carboxy-terminal lysines was necessary and sufficient to activate p21 and suppress cell growth [Tang et al., 2008].

Methylation plays both activating and repressing roles in the function of p53. Methylation at K372 stabilizes p53 and regulates expression of specific p53 target genes, therefore promoting tumor suppression [Chuikov et al., 2004]. On the other hand, methylation at K382 suppresses the transcription of highly responsive p53 target genes [Shi et al., 2007]. Ubiquitination of p53 is suppressed under stress stimuli to facilitate the formation of p53 tetramer that stabilizes the protein. It is unclear if stress such as DNA damage induces sumoylation of p53. Muller et al. [2000] reported no induction of p53 sumoylation by actinomycin D, whereas other data suggested that sumoylation of p53 was enhanced by UV or ionizing radiation (IR) [Driscoll et al., 2010]. Moreover, studies of sumoylation on p53 function have led to controversial results. Some investigators reported that sumoylation at K386 increased the transcriptional activity of p53 while others suggested no such effects. It was observed that p53 null cells transfected with sumoylation-deficient p53 had higher transcriptional activity than their counterpart transfected with wild-type p53 [Wu and Mo, 2007]. Furthermore, markedly enhanced sumoylation of p53 was observed in multiple specimens from myeloma patients [Driscoll et al., 2010].

PTM events of p53 are coordinated. Evidence has suggested extensive cross-talk between various PTM events on p53. For example, methylation at K372 facilitates subsequent p53 acetylation [Kurash et al., 2008]. However, sumoylation at K386 blocks p53 acetylation [Rodriguez et al., 1999]. Taken together, investigations on the roles of p53 in cellular malignant transformation should focus on not only individual PTM event of the protein but also the cross-talk among these events of p53.

HISTONES

Histone proteins are the main protein components of chromatin. Two copies each of histones H2A, H2B, H3, and H4 are assembled into nucleosomes. Acetylation of lysine residues by histone acetyl transferases (HATs) relaxes histone–DNA association and increases gene transcription. Conversely, histone deacetylases (HDACs) remove acetyl groups and restore the tight association of DNA to histones. HDACs therefore decrease transcription activity and are commonly altered in cancer. The hypo-acetylation of H4 is correlated to the progression of breast cancer—occurring early in the progression to a malignant phenotype [Suzuki et al., 2009]. Additionally, hyper-acetylation of H3K9, H3K18, and H4K12 was associated with better prognosis of prostate adenocarcinoma [Seligson et al., 2005]. However, acetylation of H3K9 and H4K8 was reported to be higher in hepatocellular carcinoma than in normal or cirrhotic precursor lesions [Suzuki et al., 2009]. Thus, the acetylation of histone proteins regulates transcription in a site and tissue-specific manner. HDAC inhibitors including suberoylanilide hydroxamic acid (SAHA) and valproic acid are in clinical trials for cancer therapy. SAHA has been approved for cutaneous T-cell lymphoma [Olsen et al., 2007]. SAHA and valproic acid induced apoptosis and inhibited cell-cycle progression of various cancer cells [Hsi et al., 2004; Catalano et al., 2006; Stamatopoulos et al., 2010]. The molecular mechanisms of HDAC inhibitors are complex and involve numerous substrates functioning in proliferation, differentiation, and cell death [Xu et al., 2007]. These compounds may provide new insights towards the function of acetylated proteins in the development of malignant cells.

Methylation of histones commonly occurs on lysine residues of H3 at K4, K9, K27, K36, K79, and H4 at K20. Specifically, H3K4, K36, and K79 are thought to promote euchromatin formation while H3K9 and H4K20 are markers for heterochromatin [Ellis et al., 2009]. Changes in levels of gene transcription led by methylation of histones are often seen in cancer. For example, coactivator-associated arginine methyltransferase 1 (CARM1) enhances estrogen receptor α responsive transcription activation through specific methylation of H3 [Yadav et al., 2003]. CARM1 is over-expressed in breast tumors and increased estrodiol-induced transcription has been observed in the MCF-7 breast cancer cells [Zhang et al., 2005b]. It will be interesting to deduce whether the function of CARM1 in response to estrogen is able to methylate non-histone proteins as well.

Radiation induces monoubiquitination of H2A and H2B. Such ubiquitination might be involved in the breast cancer susceptibility gene 1 (BRCA1) pathway of DNA repair. Recent reports suggest that the BRCA1 repair complex interact with CCDC98 and RAP80, and is recruited to the DNA damage site. Furthermore, these studies showed that ubiquitinated H2A and H2B accumulated and interacted with RAP80 at the DNA damage site upon radiation [Wu and Mo, 2007].

Current investigations have suggested that the PTMs of histones are associated with cancer progression. Clinical studies have been conducted on some of HDAC inhibitors in cancer patients.

PCNA

Proliferating cellular nuclear antigen (PCNA) is a trimeric ring-shaped protein that participates in many essential cellular processes such as DNA replication, repair of DNA damage, and cell-cycle progression. Studies have suggested that PCNA is post-translationally modified although the forms of PCNA PTMs are still subjects of open discussion [Naryzhny and Lee, 2004]. A cancer-associated isoform of PCNA (caPCNA) was identified that contained an unusual pattern of methyl ester groups on numerous glutamic and aspartic acid residues within PCNA [Hoelz et al., 2006]. A unique antibody was developed that specifically detected caPCNA to be applied to immunostaining studies in clinical breast cancer tissues. The caPCNA isoform may serve as an effective biomarker for breast cancer detection [Malkas et al., 2006].

Monoubiquitination of PCNA is involved in translesion synthesis of DNA replication in response to DNA damage. In order to restart DNA synthesis after the replication fork is stalled, alternative repair proteins such as Y-family DNA polymerases are required to bypass the lesion to resolve the replication stop at the damage site [Friedberg et al., 2005]. Studies demonstrated that upon UV damage PCNA is monoubiquitinated at K164 and the Y-family DNA polymerase is recruited to the damage site [Hoege et al., 2002]. It was suggested that ubiquitinated PCNA had an increased affinity to Y-family DNA polymerases, which led to the switch of polymerases. However, the induction of PCNA ubiquitination is not entirely clear and replication protein A (RPA) may be involved [Bienko et al., 2005].

Further investigations will help clarify the roles of these biochemical and molecular events of PCNA in cellular malignant transformation and progression. This knowledge could then be applied in the development of cancer biomarkers and therapeutics.

Rb

The retinoblastoma protein (Rb) is a tumor suppressor and plays fundamental role in cell regulation. In its dephosphorylated state, Rb is active and bound to E2F, a family of transcription factors regulating genes required for the progression of cell cycle through G1 and entry into the S phase. Many cancer cell types are defined by a loss of the function of p16 tumor suppressor, which activates the cyclin D/cdk4 complex, leading to the phosphorylation of Rb and the release of E2F. Binding to the promoters of cell-cycle regulated target genes, E2F activates their transcription [Liggett and Sidransky, 1998]. Efforts have been undertaken to knockdown proteins in the Rb pathway to prevent formation of phosphorylated Rb isoforms for therapeutic purpose. Small molecule inhibitors towards cyclin D/cdk4 such as thieno[2,3-d]pyrimidin-4-yl hydrazone analogues have been studied. These molecules have been reported to selectively inhibit cdk4 and exhibit cytotoxicity in HCT116 human colon carcinoma cells [Horiuchi et al., 2009]. Overall, these studies suggest that inhibiting phosphorylation of Rb should be considered in anticancer therapeutics.

STAT3

Signal transducers and activators of transcription 3 (STAT3) belongs to a family of transcription factors that regulate cell growth, differentiation, and proliferation. In its inactive form, STAT3 remains in a monomeric state in the cytoplasm. Upon cytokine stimulation, Janus kinase 2 (JAK2) phosphorylates STAT3 at tyrosine residues, which leads to the dimerization of STAT3 via reciprocal interactions between the SH2 domain of one monomer and the phosphorylated tyrosine of the other. The dimers are translocated into the nucleus where they recognize specific DNA-binding sites and activate target gene transcription [Aaronson and Horvath, 2002].

STAT3 plays an integral role in modulating oncogenesis, inhibiting apoptosis, and suppressing immunity. STAT3 has been found to be activated in 50–90% of various malignant tumors, including 53% of anaplastic astrocytomas and 53% of glioblastomas [Humphries et al., 2009]. The multi-targeted receptor tyrosine kinase inhibitor sunitinib (Sutent) has been reported to inhibit phosphorylation of STAT3. In human medulloblastoma cells, Sunitinib induces apoptosis and cell-cycle arrest, and inhibits cell growth [Yang et al., 2010]. Furthermore, Sutent shrank murine renal tumor xenografts in animals [Xin et al., 2009] and has been approved for the treatment of advanced renal cell carcinoma and imatinib-refractory gastrointestinal stromal tumors [Chow and Eckhardt, 2007; Faivre et al., 2007]. Studies revealed that the mechanisms of action of sunitinib in inducing apoptosis were complex and involved in the activation of caspase-3, the cleavage of poly(ADP-ribose) polymerase and the up-regulation of pro-apoptotic genes, *Bak* and *Bim*. The effects of Sutent on cell-cycle progression was attributed to its actions on down-regulating cyclin E, cyclin D2, and cyclin D3, and up-regulating p21Cip1 [Yang et al., 2010]. These findings have provided helpful information for the development of more potent STAT3 inhibitors.

CREB

cAMP response element-binding protein (CREB), a substrate of cAMP-dependent protein kinase, regulates gene transcription responses to diverse signals initiated by hormones and neurotransmitters. CREB consists of three major elements: a DNA-binding domain, a leucine zipper responsible for dimerization, and a transactivation domain that contains a number of phosphorylation sites [Meek and Street, 1992]. CREB appears to be constitutively bound to DNA, but is only fully activated upon phosphorylation at serine 133, promoting its association with the co-activators CBP and p300 [Johannessen et al., 2004]. Studies suggested a correlation between CREB and tumor progression. It was revealed that a CREB-binding site was in the promoter region of MUC 18, a marker for melanoma invasion and progression. Silencing of G protein coupled receptor PAR1 with shRNA down-regulated the expression of MUC18 and also decreased the level of phosphorylation of CREB at serine 133 [Melnikova et al., 2009]. The results suggest that CREB plays an important role in regulating MUC18 in the metastatic pathway for melanoma cells.

Over-expression of CREB has been correlated with acute myeloid leukemia (AML). Western blot-analysis of cell lysates from AML patients showed a two- to three-fold increase in the phosphorylation levels of CREB when compared to non-malignant cell lysates. The studies indicated that the over-expression of CREB was probably not enough to induce AML but could lead to the myeloproliferative disorder in vivo and also that the phosphorylation/activation of CREB might serve as a biochemical marker for AML relapse [Shankar et al., 2005].

Although down-regulating proteins upstream of CREB phosphorylation pathway to inhibit its activity is appealing, such a strategy would be taken with a great risk since G proteins and kinases have multiple levels of cross-talk with molecules in other pathways. Direct inhibition of phosphorylated CREB (pCREB) interaction with its co-activators has more advantages in modulating its activity. KG501 was reported to disrupt the interaction of pCREB with its co-activator CBP [Best et al., 2004] and decrease the expression levels of pro-angiogenic CXC genes in non-small lung cancer cells. Sequence analysis of CXC genes revealed binding sites for CREB and moreover, down-regulation of CREB caused reduced levels of CXC gene expression [Sun et al., 2008], indicating that KG501 may be useful in preventing lung cancer metastasis.

More studies are required to investigate the correlation between cancer relapse and phosphorylation of CREB and evaluate the anticancer effects of targeting the PTM form of CREB.

c-Myc

c-Myc is an oncoprotein that serves as a transcription regulator to control cell growth and differentiation. c-Myc recruits HATs to chromatin to increase the transcription of target genes and is also acetylated by several HATs (CBP, Tip60, Gcn5, and PCAF) at various lysine residues, which prevents c-Myc from ubiquitination and proteasomal degradation. However, acetylation of c-Myc by p300 enhanced c-Myc degradation [Zhang et al., 2005a]. Over-expression and increased acetylation of c-Myc are prevalent in human cancers. Pulse-chase experiments demonstrated that c-Myc turnover in Burkitt's lymphoma-derived cell lines was two- to six-fold more prolonged compared to the half-life of c-Myc in Epstein–Barr virus (EBV)-immortalized B cells, suggesting that the regulation of c-Myc stability through acetylation may play an important role in the development of Burkitt's lymphoma [Gregory and Hann, 2000].

SUMMARY AND FUTURE DIRECTION

PTMs of nuclear proteins are involved in the regulation of gene transcription and other nuclear molecular processes. This paper reviews the correlation of specific isoforms of various nuclear proteins with cellular malignant transformation and progression, and also the progress in developing compounds to inhibit the functions of these PTMs in cancer cells. More studies are required to explore the cross-talk among these PTM events in order to fully understand their roles in cancer biology. Future research may open up new areas in the field of clinical oncology by promoting the identification of specific PTMs of nuclear proteins as cancer biomarkers and facilitating the development of small molecules to inhibit their functions for cancer chemotherapy.

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