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Post-translational Modifications (PTMs), from a Cancer Perspective: An Overview

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ABSTRACT

Studies on post-translational modifications (PTMs) have grabbed attention of the scientific community worldwide, its role in pathogenesis of cancer and prognostic biomarkers associated with cancers. However, unraveling the specific role of PTMs in carcinogenesis or in predictive biomarkers requires holistic understanding of the cancer types and associated mechanisms. Manifestation of cancer is complex and involves multiple steps including modifications at the levels of genes, associated proteins and signaling pathways. Biomarkers, as a prognostic marker, are critical in deciding efficacy of the clinical outcomes in malignancies. Growing evidence suggests that several biomarkers that are post-translationally modified play important role in human cancers. In the current review, few of such biomarkers and targets that are post-translationally modified and are associated with carcinogenesis are collated and analyzed to provide a bird's eye view of their role in cancer types. Such analysis will help in understanding the pathogenesis and the precise role of biomarkers in designing better therapeutic interventions for different cancer types.

KEYWORDS: Cancer Markers; Oncoproteins; Kinase; Phosphorylation; Methylation

METHODS

The writing of this review involved a comprehensive search of original articles and reviews published on the subject of post translational modifications. Free search engine PubMed was used to conduct the online search. Sorting option 'Best Match' of PubMed was used to conduct the more relevant search. Various expressions were used to find relevant references for example, "post translational modifications in cancer", "acetylation in cancer and post translational modifications", "methylation in cancer and post translational modifications", "biomarkers in cancer" etc. Some other expressions were used to conduct a more specific search to complement the findings in the articles retrieved with the more general search criteria for example, "checkpoint kinase 1 in cancer", "candidate tumor suppressor BTG3" etc. Further, some articles were also found through reading of previous reviews on similar subjects including the ones by Karve and Cheema [1], and Han et al, [2]. Articles clearly related to the theme of this review and those that matched the search criteria were selected according to their year of publication (only articles published after 2000 were included in this review, except in specific situations) and relevance to the aims of this review.

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INTRODUCTION: Clinically relevant post-translational modifications (PTMs)

'Omic' technologies (genomics, transcriptomics, proteomics and metabolomics) have evolved rapidly over the last decade. Evolution of these technologies has offered ample potential in the hunt for molecular markers of early stage cancers. However, these methods can be insufficient to investigate the dynamic nature of signaling processes that cells exhibit during their transformation to become tumor [3].

During the transformation of a cell from normal to neoplastic (tumorous) many important signaling events takes place which are controlled by the diverse realm of post-translational modifications (PTMs) [4]. PTMs are one of the critical regulatory mechanisms of cells affecting a number of biological functions. Various proteins are controlled by PTMs which are, in general, reversible. Since 2000, >54K articles on PTMs have been published as per the data obtained from PubMed. More than 450 unique protein modifications have been identified till date [2], including acetylation, methylation, phosphorylation, SUMOylation and ubiquitination, all of these PTM types can modify the activity of target proteins.

PTMs offer an abundance of potential candidates for biomarker detection hence PTMs related to these biomarkers should well be pursued for development of promising surrogate markers. Applications of many forms of PTMs have been identified in cancer medicine, however, for several other PTM types, applications are not yet readily apparent. It is worthwhile to explore different types of PTMs as they may prove valuable in near future to improve our understanding of carcinogenesis and fight against it. This review focuses on recent advancements in our understanding of various PTMs in the perspective of carcinogenesis. Some of the prominent proteins and associated PTMs relevant to carcinogenesis investigated by many laboratories are highlighted in Table 1.

Table 1: Post-translational modifications (PTMs) associated with proteins causative to oncogenesis

Protein	Post-translational Modification (PTM) Type	General Expression Pattern in Cancer	Reference
NF-kB	Acetylation	Overexpressed	[5]
LDH-A		Overexpressed	[6]
p53		Under-expressed	[7]
GP73	Glycosylation	Overexpressed	[8]
MUC1		Overexpressed	[9]
MUC16		Overexpressed	[10]
CD44		Overexpressed	[11]
GPCR	Methylation	Overexpressed	[12]
HMGB1		Overexpressed	[13]
RIOK1		Overexpressed	[14]
CHK1		Overexpressed	[15]
UBE2F	Neddylation	Overexpressed	[16]
HuR		Overexpressed	[17]
PTEN	Phosphorylation	Under-expressed	[18]
STAT-3		Overexpressed	[19]
Osteopontin		Overexpressed	[20]
EGFRs		Overexpressed	[21]
AKT		Overexpressed	[22]
p53		Under-expressed	[23]
DAPK1		Overexpressed	[24]
Rho	Prenylation	Overexpressed/Under-expressed	[25]
Ubc9	SUMOylation	Overexpressed	[26]
FOXK2		Under-expressed	[27]
HIC1		Under-expressed	[28]
CHK1	Ubiquitination	Overexpressed	[29]
p53		Under-expressed	[30]

Acetylation

Acetylation has emerged as a dynamic post translational modification that plays a key role in regulating nuclear transcription and metabolic homeostasis [33]. It mediates regulation of cellular processes, intermediary metabolism and metabolic enzymes via enzymatic activation or inhibition and further influence protein stability. Acetylation reactions are catalyzed by various N-terminal (NAT) and lysine acetyltransferases. Lysine acetylation, in particular, is enzymatically reversible and is tightly regulated by metabolism-dependent mechanisms.

Our understanding of protein acetylation has increased significantly in recent years by global proteomics analyses. Kim et al, [34] conducted the first proteomic survey for the acetylation modification and identified 388 acetylation sites in 195 proteins among the proteins derived from HeLA cells and mouse liver mitochondria. A comprehensive characterization of protein acetylation dynamics using mass spectrometry (MS) based proteomics revealed around 1,000 sites with significantly increasing acetylation trends [35].

Acetylation and deacetylation interplay is the key for many important cellular processes, malfunctioning in this machinery can result in severe conditions such as cancer, neurodegenerative diseases and cardiovascular disorders [36,

37]. Acetylation specific site mutations are enriched in cancer with decreased patient survival [38]. A recent study found 2106 acetylation-related single nucleotide variants (SNVs), 6405 ubiquitination-related SNVs, and 883 SNVs in shared sites of the two PTMs, covering cancer samples of various types, in this study, several known oncoproteins (TP53, AKT1 and IDH1) were shown to be modified for acetylation in cancer [38].

Histone deacetylases (HDACs) are involved in the deacetylation of not only histone proteins but non-histone proteins as well, regulating important functions. Studies have indicated that HDACs can regulate the expression of genes by direct interaction with transcription factors such as E2f, Stat3, p53 etc. [39]. Altered HDAC activity is linked to tumor development, identifying HDACs among one of the most promising biomarkers/targets in cancer research. Vorinostat, the first FDA-approved HDAC inhibitor, is used in the treatment of relapsed and refractory cutaneous T-cell lymphoma (CTCL) [40].

Acetylation has many important effects on oncoprotein p53, it increases p53 protein stability. In many cell types, inhibition of HDACs that remove acetyl groups from p53 (i.e., HDAC1 and SIRT1) causes increased p53 acetylation and p53-dependent activation of apoptosis and senescence [41]. Acetylation is an essential regulator of the anti-cancer functions of p53 [42]. In a study it was deduced that temporary and reversible inhibition of p53 acetylation in cancer subjects, especially those with p53-mutant tumors, may protect them from severe chemotoxicity [7].

It has been shown that expression of NATs may both be increased and decreased in cancer versus non-cancer tissues and these acetyltransferase enzymes have been suggested to act as oncoproteins as well as tumor suppressors in human cancers [37]. Acetylation is an important modification of proteins with effects on the metabolome level and is an important research area to understand its physiological consequences.

Methylation

Methylation is a comparatively budding and promising area of research which has emerged as a prevalent post-translational modification. Methylation of arginine/lysine residues on non-histone proteins frequently mediates the transduction of cellular signals. With recent technological advancements the stage is now set to decode the 'methylproteome' to delineate its functions in health and disease [43].

Methylation of non-histone protein has an important regulatory role to play in a wide range of cellular processes [44] including transcriptional regulation, RNA metabolism and DNA damage repair. Various proteins involved in DNA repair (MRE11, p53, DNA polymerase b) have been shown to be controlled by arginine/lysine methylation [45].

With growing number of lysine methyltransferases (methylate non-histone proteins on lysine residue), a number of proteins like ERα, NF-κB, pCAF and other transcription factors have been identified that have implications in tumorigenesis and other metabolic disorders [1]. In addition to regulating gene expression, protein modification by methylation also contributes to the regulation of protein stability [46]. In a recent study, it was highlighted that BTG3 (B-cell translocation gene 3), a candidate tumor suppressor, promotes methylation of CHK1 (checkpoint kinase 1), a vital checkpoint kinase essential to normal cellular functions [15]. CHK1 has also been shown to be methylated in response to ultraviolet-induced DNA damage [47].

DNA methylation, catalyzed by DNA methyltransferases (DNMTs), is an important epigenetic modification. Plentiful studies have examined expression of DNMTs in tumor tissues, especially expression of DNMT1 [48, 49]. PTMs play a crucial role in determining the correct functions of DNMT1. Altered role of DNMT1 results in aberrant methylation patterns which may initiate tumor formation. Presently, possibilities of DNMT1 as a new target for many tumors including breast cancer are being explored.

Arginine/lysine residues methylation is dynamic and reversible which can be removed by demethylation enzymes [50]. Identification of mechanisms involved in protein methylation/demethylation remains an interesting area of research to understand the regulatory roles of target proteins in cancer and other diseases.

Phosphorylation

Phosphorylation is one of the most prominent PTM of proteins and is an important cellular regulatory mechanism as through phosphorylation and dephosphorylation events many proteins, enzymes and receptors are regulated. Phosphorylation is a reversible mechanism and regulates numerous cellular processes such as protein synthesis, cell division, signal transduction, cell growth, development and aging which happen through protein kinases and phosphatases. Especially, the protein kinases are accountable for cellular transduction signaling and their overexpression or malfunction is found in several diseases, mostly tumors [51]. Therefore, targeting protein kinases using kinase inhibitors can be valuable for the treatment of cancer. The most common

amino acid residues modified for phosphorylation are serine (Ser or S), threonine (Thr or T), and tyrosine (Tyr or Y), they also play indicative role in progression of cancer [18, 52].

A number of cellular signalling pathways including tyrosine kinase, MAP kinase, cadherin–catenin complex and others are major players of the cell cycle, and deregulation in their phosphorylation-dephosphorylation cascade has been shown to be manifested in the form of various types of cancers [53]. Phosphorylation of Akt/protein kinase B (PKB), a serine/threonine kinase which mediates a variety of biological responses, has a prognostic and/or predictive role of in several cancers including breast, prostate and non-small cell lung cancer [54]. Dysregulated tyrosine kinase activity is reported in different types of cancers for example amplification of Her2/neu was observed in tumor cells of breast cancer [55]. MAPK cascade (SOS-Ras-Raf- MAP kinase pathway), involved in the regulation of normal cell proliferation, differentiation and apoptosis, has an important role in cancer growth and progression [56].

Additionally, the importance of Raf and MEK in cancer progression and in promoting cancer growth has been well established [57]. Tumor suppressor p53 phosphorylation sites, Ser315 and Ser392 in the C-terminal regulatory domain, are associated with elevated p53-dependent transcription [58]. During DNA damage, expression of proapoptotic protein Bax, members of the Bcl-2 (B-Cell Lymphoma 2) family of proteins, is upregulated by the protein p53. Such apoptotic pathways are the focus of cancer researchers to develop new drugs.

To sustain the functional integrity of the cadherin–catenin complex phosphorylation is an important process. Dysregulation of this process has been found to be strongly associated with cell-adhesion defects in carcinomas including prostate cancer progression [53,59]. Studies have revealed that transforming growth factor β (TGF β) prevents the phosphorylation of retinoblastoma protein (pRb) which leads to its inactivation [60]. This signaling is altered in many human cancers [61], in some of which impassiveness of cyclin-CDK4 complex to the inhibitory signals of p15INK4B leads to inactivation of pRb by hyperphosphorylation [62].

Phosphorylation pathways are crucial regulators of normal cellular functioning and these pathways are needed to be considered for more rational treatment of cancer.

SUMOylation

SUMOylation is a widely occurring reversible PTM which has attracted increasing attention as it is involved in a number of biological processes for the maintenance of genomic integrity. Small ubiquitin-like modifier (SUMO) is structure wise similar to that of ubiquitin and is covalently attached to lysine residues of specific target proteins [63], SUMO1, SUMO2/3 and SUMO4 are the identified SUMO isoforms. SUMO pathway is conserved in all eukaryotes and plays pivotal roles in the regulation of DNA damage repair, gene expression, cellular signaling, cell cycle progression and apoptosis. Irregular SUMOylation can lead to the progression of a number of diseases, including cancer. The vital role of SUMOylation in tumorigenesis has gradually emerged [64].

Studies have shown that SUMOylation plays an important role in cancer [64] and many oncogenes and tumor suppressors are functionally regulated via SUMOylation [65]. BRCA1, a tumor suppressor gene in humans associated with breast and ovarian cancer is modified by SUMO in response to genotoxic stress, and co-localizes at sites of DNA damage with SUMO1, SUMO2/3 and the SUMO-conjugating enzyme Ubc9 [66].

SUMOylation has varied effects on transcriptional activity of androgen receptor (AR) which has an established role in prostate carcinogenesis [67]. SUMO-resistant DNA endonuclease, Mus81 mutants involved in homologous recombination repair, display compromised DNA damage responses associated to tumorigenesis [68]. An important SUMO-conjugating enzyme in the SUMOylation pathway, Ube2I, SUMO-inducer ARF and the SUMO-ligase PIAS1 were seen greater than normal levels in multiple myeloma patients [69].

Tumor suppressor p53 promotes cellular senescence as well as apoptosis. SUMO-1 conjugation with p53 has been shown to result in p53 stabilization and activation, causing the induction of senescence [70]. DNA damage signals or oncogenic mutations induce SUMO disorders that ultimately lead to cell senescence, effects of this on tumor or tumor microenvironment is the current focus of research.

SUMO modification, as an important PTM, is a key to regulating cell activities. It has been accepted and confirmed by research that SUMO modification plays a vital role in the pathological processes. SUMO modification is linked with tumorigenesis and targeting SUMO pathways could be exploited in anticancer therapies.

Ubiquitination

Ubiquitination, as a multistep, conserved and highly dynamic process, functions to degrade and recycle proteins. It is involved in additional cellular processes such as activation of NFkB inflammatory response and DNA damage repair [71]. Ubiquitination also affects the result of many lethal

diseases like cancer [72]. Three main classes of ubiquitination enzymes are activating enzymes (E1), conjugating enzymes (E2), and ligases (E3). Unregulated expression of these enzymes, including DUBs (deubiquitinating enzymes) and other complexes (SCF complex) involved in ubiquitination mechanism, contributes to the signaling of various oncogenes leading to cancer progression and metastasis.

Ubiquitination displays parallel properties with phosphorylation but distinguishes itself in important ways [73]. As a marker, phosphorylation often triggers subsequent ubiquitination, in particular where ubiquitination leads to degradation [74], and in other cases ubiquitination provide a switching mechanism that can turn on/off the kinase activity of certain proteins [75]. Hence, understanding the crosstalk between these important PTMs is crucial to explore how they regulate signal transduction.

Various studies have shown that E2 ubiquitin conjugating enzymes (for example UBE2N and UBE2C) are associated with aberrant oncogenic signaling of numerous molecules including inflammatory NFkB and TGFb, receptor tyrosine kinases and others [76,77,78]. Like E2 ubiquitin conjugating enzymes, altered expression of E3 ubiquitin ligases also leads to aberrant oncogenic signaling [71]. For example, enhanced expression of STIP1 Homology and U-Box Containing Protein 1 (STUB1), an E3 ligase, is found to be associated with pancreatic, prostate and other cancer types [79]. DUBs are also important players of cellular processes such as DNA repair and cell cycle progression. Several studies have shown that altered than normal role of DUBs is involved with cancer progression [80,81,82]. It is clear that various enzymes involved in ubiquitination are linked with cancer progression hence there is need to develop therapeutic agents targeting these enzymes to counter the oncogenic pathways.

PTMs based Cancer Markers

The understanding of mechanisms of PTMs has contributed to the identification of new biomarkers which are of relevant to clinical practice, enabling researchers to use targeted therapeutic approaches in the treatment of cancer. Specific inhibitors are being developed and testing of such inhibitors against target protein may prove to be effective in targeting certain types of cancer. The significance of crosstalk between different types of PTMs has been well recognized and targeting one or the other modification has been the focus area of cancer research.

Discovery of novel anticancer drugs is critical for treating patients. This search of anticancer compounds is based on the genes, associated proteins and pathways which have been implicated in tumorigenesis. For example, in a recent study, a comparative global methylation profiling resulted in identification of 7 hyper-methylated (e.g., FBN1, LPP, and SOD3) and 61 hypo-methylated (e.g., HBE1, SNRPF, TPD52) markers for gallbladder cancer (GBC) [83]. Oncology drugs approved lately, target distinct cancer biomarkers or pathways in tumor cells. Table 2 lists some examples of the important cancer biomarkers, all of them are known to be post-translationally modified, and effectively targeted for the development of drugs. We have briefly discussed below some PTM based biomarkers associated with carcinogenesis.

Table 2: Validated targets approved as cancer therapy and prognostic markers

Cancer Biomarker	Indication	Drug[a] (Company)
EGFR	Lung Cancer	Iressa/Gefitinib (Astra-Zeneca)
KRAS	Colorectal Cancer	Erbitux/Cetuximab (Eli Lilly)
HER2	Breast Cancer	Herceptin/Trastuzumab (Genentech)
BRAF	Melanoma	Mekinist/Trametinib (Novartis)
BCL-2	Leukemia	Venclexta/Venetoclax (AbbVie/Genentech)
CD117 (KIT)	Gastrointestinal Tumors	Gleevec/Imatinib Mesylate (Novartis)
ALK	Non-Small Cell Lung Cancer	Zykadia/Ceritinib (Novartis)
PI3K Delta	Lymphoma	Zydelig/Idelalisib (Gilead)
DNMT1	Leukemia	Natdecita/Decitabine (Natco)
SMO	Basal Cell Carcinoma	Erivedge/Vismodegib (Genentech)

[a]Most of these drugs are recommended with companion diagnostics (CDx)

PTMs directly modulate the cellular signaling and trafficking of an important cell component, epidermal growth factor receptor (EGFR). EGFR is an important cancer biomarker owing to the molecular events associated with cancer. EGFR protein-protein interactions and PTMs are responsible for its signaling and trafficking which have been extensively studied [84]. Upon X-rays and chemotherapy treatments, EGFR becomes phosphorylated and this event is accompanied by receptor internalization provoking p38 or Src-dependent, and clathrin- and AP-2 adaptor-dependent endocytic trafficking [85,86,87]. It has been shown that abolishing p38-dependent EGFR internalization diminishes the efficacy of chemotherapy-

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induced cell death therefore promoting the cytotoxic effect of chemotherapy drugs such as Cisplatin [87]. Drugs, for example Gefitinib (Iressa) and Erlotinib (Tarceva), has been approved with either a companion or complementary diagnostic to target activating EGFR mutation (EGFR M+) in non-small cell lung cancer (NSCLC). Mutations involving the PTM sites of EGFR impair EGFR trafficking. EGFR sites, tyr1068 and tyr1173, are among the two most relevant phosphorylation sites of EGFR, and phosphorylation at tyr1068 has been identified as a powerful biomarker associated with strong Erlotinib sensitivity in lung cancer stem cells (LCSCs) [21]. In contrast, a recent study provided additional mechanistic aspects of EGFR regulation by showing that mutations preventing EGFR phosphorylation at tyr998 or in the ser1039 region abolished or greatly reduced EGFR interactions with Adaptin subunits AP-2 and AP-1, and resulted in impaired receptor trafficking [88]. Studying the biological effects of such events are is important to determine the efficacy of EGFR-targeting drugs.

Human epidermal growth factor receptor-2 (HER2) is another important cancer biomarker which is overexpressed in large number of breast cancers. HER2 is activated by phosphorylation at specific tyrosine residues. Strong expression of activated HER2 is associated with poor prognosis in HER2 positive breast cancer patients. Experiments on primary breast tumors showed that strong expression of HER2 phosphorylated at tyrosine 1221/1222 is associated with poor prognosis in HER2 positive breast cancer patients [89].

To treat HER2 positive breast cancer patients, drug Trastuzumab (Herceptin) is used which inhibits HER2 signaling and its subsequent activation. Inception of companion diagnostics was with Herceptin. Herceptin mechanism involves inhibition of HER2 cleavage and prevention of the production of an active truncated HER2 fragment [90]. However, Herceptin resistance has been noted in some patients possibly due to failure to abolish HER2 phosphorylation, therefore, alternate treatment opportunities are also being explored to overcome acquired resistance in breast cancers. Studies have confirmed that Herceptin although down-regulated HER2 receptors in HER2-positive breast cell lines but failed to decrease HER2 phosphorylation as this phosphorylation was maintained and increased by the ligand-induced activation of EGFR, HER3, and HER4 receptors, resulting in their dimerization with HER2, by a protein kinase B (PKB) negative feedback loop [91]. Similar feedback loops might also be involved in the acquired resistance to Herceptin, an area of further research.

Physical blockade of the HER2 receptor is a further proposed mechanism for Herceptin resistance, for example, the mucin molecule, MUC4, with its extended carbohydrate structure seems to function as a barrier for biomolecular interactions in the extracellular environment [92,93]. A recent study highlighted the importance of cellular glycosylation on the binding of the drug Herceptin to the surface of cancer cells, the responsiveness of cancer cells to a chemotherapeutic agent, and potential of glycosylation inhibitors as future combination treatments for breast cancer [94]. This study showed the importance of the glycocaylx in the accessibility of the HER2 epitope to Herceptin [94], influencing many aspects of cancer cell biology and drug responsiveness since glycosylation affects many proteins.

Abnormal protein glycosylation is a well-known event in oncogenesis which modulates the response of cancer cells to chemotherapeutic and biological treatments. Glycoproteins and/or altered tumor-associated carbohydrate antigens are targeted and recognized by many currently employed antibodies that recognize commonly occurring alterations in neoplastic cell antigens. Several of these glycobiomarkers including cancer antigens, mucins, integrins, HER2, and other tumor-associated glycoproteins are currently in use for management of human cancers [95]. With modern studies, it is clear that glycan-markers give us the opportunity to use them as a tag for recognition and possible targeting of tumors. Glycobiomarkers, for example, mucin-type O-glycans Tn and its sialylated version STn carbohydrate antigens, expressed highly by many types of tumors, may serve not only as a prognostic marker but also as a therapeutic target [96]. Not only as a biomarker but also as a contributor to the cancer development, protein glycosylation is an important phenomenon. It is therefore imperative to explore tumor-associated glycosylation as it provides novel diagnostic and therapeutic targets.

Estrogen receptor α (ERα) is expressed in the majority of breast cancers and promotes estrogen-dependent cancer progression. Redox- and phosphorylation-based PTMs are important and common modifications of ERα along with several other reported ERα PTMs, many of these modifications modulate receptors activity in breast tumors [97]. Important phosphorylation sites have been identified in endogenous ERα derived from the human breast cancer cell lines [97]. Phosphorylation of ERα induced by a growth factor pathway might be one mechanism of enhanced activation of the estrogen signal [98], for example, sites targeted by kinases such as MAPK, Akt, and c-Src [99]. ERα degradation by ubiquitin-ligase activity is another important factor controlling ERα signaling. It has been suggested that E3 ubiquitin ligase

ring finger protein 31 (RNF31) and p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4) might be useful therapeutic targets in ERα-positive breast cancer. Both RNF31 and PAK4 act as modulator of ERα protein level by means of ubiquitination and phosphorylation mechanisms, respectively [100,101]. Alterations contributing to increased activity, and diminished degradation of ERα protein are likely to contribute to the pathogenesis of ERα-positive breast tumors.

Ubiquitously expressed E3 ligase protein cereblon (CRBN) has been emerged as a therapeutically important cancer biomarker in hematological malignancies. Drugs like Thalidomide and its second generation derivatives, Lenalidomide and Pomalidomide, have been approved to target CRBN by preventing its auto-ubiquitination [102].

A number of proteins have been identified to be associated with tumorigenesis directly or indirectly. Exploration of the effects of various PTMs on these proteins and further dissection of their mechanisms of actions will help in identification of novel cancer biomarkers and will also pave the way for newer therapeutic opportunities to target cancer. Nevertheless, noteworthy advancements have been made in the search for biomarkers related to PTMs and cancer. However, targeting of these biomarkers and associated pathways remains challenging.

Conclusion and Future Perspectives

With new PTMs being unraveled, more and more proteins are being discovered to be involved in the pathogenesis of multiple diseases including cancer. The broad spectrum of PTMs imparts both metabolic and non-metabolic benefits to cancer cells. It is crucial to understand the key mechanisms associated with PTMs and their pathways, and also the crosstalk between various PTMs which will eventually expand our understanding to refine the clinical targeting of cancer biomarkers linked with PTMs and to contribute towards drug development for the treatment of cancers. Systematic identification along with functional and mechanistic characterization of PTMs of target proteins would aid in the development of innovative strategies for drug discovery and cancer therapy.

Better understanding of cancer dependency on PTMs and to anticipate the associated molecules and pathways is one of the major challenges in the future drug discovery. Overall good clinical response with current and new drugs under investigations is seen, however, with the emerging drugs, their resistance is also growing. This emerging resistance is another challenge scientists are weathering. Understanding resistance mechanisms will lead to deeper understanding of carcinogenesis and will also pave the way to discover new generation drugs with profound selectivity to overcome resistance. With new drugs, a large number of clinical trials will also be warranted to validate the efficacy of drugs.

Factual state of cancer progression may not be completely reflected by simply observing the changes in gene expression levels therefore it is important to study PTMs to find out the differences between normal and cancer tissues. Further study and evaluation of various functional modifications of proteins and their role in biological pathways will be instrumental in broadening the avenue of translational medicine for deadly diseases like cancer.

REFERENCES

1. Karve TM, Cheema AK (2011) Small changes huge impact: the role of protein posttranslational modifications in cellular homeostasis and disease. J Amino Acids 2011: 207691.
2. Han ZJ, Feng YH, Gu BH, Li YM, Chen H (2018) The post-translational modification, SUMOylation, and cancer. Int J Oncol 52(4): 1081-1094.
3. Krueger KE, Srivastava S (2006) Posttranslational protein modifications current implications for cancer detection, prevention, and therapeutics. Mol Cell Proteomics 5(10): 1799-1810.
4. Blixt O, Head S, Mondala T, Scanlan C, Huflejt ME, Alvarez R, et al. (2004) Printed covalent glycan array for ligand profiling of diverse glycan binding proteins. Proc Natl Acad Sci U S A 101(49): 17033-17038.
5. Baud V, Collares D (2016) Post-Translational Modifications of RelB NF-κB Subunit and Associated Functions. Cells 5(2): 22.
6. Zhao D, Zou SW, Liu Y, Zhou X, Mo Y, Wang P, et al. (2013) Lysine-5 acetylation negatively regulates lactate dehydrogenase A and is decreased in pancreatic cancer. Cancer cell 23(4): 464-476.
7. Zheng S, Koh XY, Goh HC, Rahmat SA, Hwang LA, Lane DP (2017) Inhibiting p53 acetylation reduces cancer chemotoxicity. Cancer Res 77(16): 4342-4354.
8. Jiang K, Li W, Zhang Q, Yan G, Guo K, Zhang S, et al. (2016) GP73 N-glycosylation at Asn144 reduces hepatocellular carcinoma cell motility and invasiveness. Oncotarget 7(17): 23530-23541.
9. Nath S, Mukherjee P (2014) MUC1: a multifaceted oncoprotein with a key role in cancer progression. Trends Mol Med 20(6): 332-342.

10. Rao TD, Fernández-Tejada A, Axelrod A, Rosales N, Yan X, Thapi S, et al. (2017) Antibodies Against Specific MUC16 Glycosylation Sites Inhibit Ovarian Cancer Growth. ACS Chem Biol 12(8): 2085-2096.
11. Chen X, Nagai Y, Zhu Z, Ruan H, Peehl DM, Greene MI, et al. (2018) A spliced form of CD44 expresses the unique glycan that is recognized by the prostate cancer specific antibody F77. Oncotarget 9(3): 3631-3640.
12. Bar-Shavit R, Maoz M, Kancharla A, Nag JK, Agranovich D, Grisaru-Granovsky S, et al. (2016) G protein-coupled receptors in cancer. Int J Mol Sci 17(8): 1320.
13. Richard SA, Jiang Y, Xiang LH, Zhou S, Wang J, Su Z, et al. (2017) Post-translational modifications of high mobility group box 1 and cancer. Am J Transl Res 9(12): 5181-5196.
14. Hong X, Huang H, Qiu X, Ding Z, Feng X, Zhu Y, et al. (2018) Targeting posttranslational modifications of RIOK1 inhibits the progression of colorectal and gastric cancers. eLife 7: e29511.
15. Sharma BS (2017) BTG3, a candidate tumor suppressor, promotes methylation of checkpoint kinase CHK1. Gene Rep 7: 119-22.
16. Zhou W, Xu J, Li H, Xu M, Chen ZJ, Wei W, et al. (2017) Neddylation E2 UBE2F promotes the survival of lung cancer cells by activating CRL5 to degrade NOXA via the K11 linkage. Clin Cancer Res 23(4): 1104-16.
17. Embade N, Fernandez-Ramos D, Varela-Rey M, Beraza N, Sini M, Gutierrez de Juan V, et al. (2012) Murine double minute 2 regulates Hu antigen R stability in human liver and colon cancer through NEDDylation. Hepatology 55(4): 1237-48.
18. Chen Z, Dempsey DR, Thomas SN, Hayward D, Bolduc DM, Cole PA (2016) Molecular features of phosphatase and tensin homolog (PTEN) Regulation by C-terminal phosphorylation. J Biol Chem 291(27): 14160-9.
19. Unver N, Delgado O, Zeleke K, Cumpian A, Tang X, Caetano MS, et al. (2018) Reduced IL-6 levels and tumor-associated phospho-STAT 3 are associated with reduced tumor development in a mouse model of lung cancer chemoprevention with myo-inositol. Int J Cancer 142(7): 1405-17.
20. Wei R, Wong JP, Kwok HF (2017) Osteopontin -- a promising biomarker for cancer therapy. J Cancer 8(12): 2173-2183.
21. Sette G, Salvati V, Mottolese M, Visca P, Gallo E, Fecchi K, et al. (2015) Tyr1068-phosphorylated epidermal growth factor receptor (EGFR) predicts cancer stem cell targeting by erlotinib in preclinical models of wild-type EGFR lung cancer. Cell Death Dis 6(8): e1850.
22. Crosbie PA, Crosbie EJ, Aspinall-O'Dea M, Walker M, Harrison R, Pernemalm M, et al. (2016) ERK and AKT phosphorylation status in lung cancer and emphysema using nanocapillary isoelectric focusing. BMJ Open Respir Res 3(1): e000114.
23. Matsumoto M, Furihata M, Ohtsuki Y (2006) Posttranslational phosphorylation of mutant p53 protein in tumor development. Med Mol Morphol 39(2): 79-87.
24. Bialik S, Kimchi A (2006) The death-associated protein kinases: structure, function, and beyond. Annu. Rev. Biochem 75: 189-210.
25. Berndt N, Hamilton AD, Sebti SM (2011) Targeting protein prenylation for cancer therapy. Nat Rev Cancer 11(11): 775-91.
26. Tomasi ML, Tomasi I, Ramani K, Pascale RM, Xu J, Giordano P, et al. (2012) S-adenosyl methionine regulates ubiquitin-conjugating enzyme 9 protein expression and sumoylation in murine liver and human cancers. Hepatology 56(3): 982-93.
27. Nestal de Moraes G, Ji Z, Fan LY, Yao S, Zona S, Sharrocks AD, et al. (2018) SUMOylation modulates FOXK2-mediated paclitaxel sensitivity in breast cancer cells. Oncogenesis 7(3): 29.
28. Paget S, Dubuissez M, Dehennaut V, Nassour J, Harmon BT, Spruyt N, et al. (2017) HIC1 (hypermethylated in cancer 1) SUMOylation is dispensable for DNA repair but is essential for the apoptotic DNA damage response (DDR) to irreparable DNA double-strand breaks (DSBs). Oncotarget 8(2): 2916-2935.
29. Cheng YC, Lin TY, Shieh SY (2013) Candidate tumor suppressor BTG3 maintains genomic stability by promoting Lys63-linked ubiquitination and activation of the checkpoint kinase CHK1. Proc Natl Acad Sci U S A 110(15): 5993-8.
30. Ge Z, Leighton JS, Wang Y, Peng X, Chen Z, Chen H, et al. (2018) Integrated Genomic Analysis of the Ubiquitin Pathway across Cancer Types. Cell Rep 23(1): 213-226.
31. Wang Q, Gao G, Zhang T, Yao K, Chen H, Park MH, et al. (2018) TRAF1 is critical for regulating the BRAF/MEK/ERK pathway in non-small cell lung carcinogenesis. Cancer Res 78(14): 3982-3994.
32. Bisogno LS, Friedersdorf MB, Keene JD (2018) Ras post-transcriptionally enhances a pre-malignantly primed EMT to promote invasion. iScience 4: 97-108.
33. Park JM, Jo SH, Kim MY, Kim TH, Ahn YH (2015) Role of transcription factor acetylation in the regulation of metabolic homeostasis. Protein Cell 6(11): 804-13.

34. Kim SC, Sprung R, Chen Y, Xu Y, Ball H, Pei J, et al. (2006) Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol cell 23(4): 607-18.
35. Kori Y, Sidoli S, Yuan ZF, Lund PJ, Zhao X, Garcia BA (2017) Proteome-wide acetylation dynamics in human cells. Sci Rep 7(1): 10296.
36. Haberland M, Montgomery RL, Olson EN (2009) The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 10(1): 32-42.
37. Kalvik TV, Arnesen T (2013) Protein N-terminal acetyltransferases in cancer. Oncogene 32(3): 269-76.
38. Narayan S, Bader GD, Reimand J (2016) Frequent mutations in acetylation and ubiquitination sites suggest novel driver mechanisms of cancer. Genome Med 8(1): 55.
39. Lin HY, Chen CS, Lin SP, Weng JR, Chen CS (2006) Targeting histone deacetylase in cancer therapy. Med Res Rev 26(4): 397-413.
40. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al (2007) Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 109(1): 31-9.
41. Brooks CL, Gu W (2011) The impact of acetylation and deacetylation on the p53 pathway. Protein Cell 2(6): 456-62.
42. Reed SM, Quelle DE (2014) p53 acetylation: regulation and consequences. Cancers (Basel) 7(1): 30-69.
43. Biggar KK, Li SS (2015) Non-histone protein methylation as a regulator of cellular signalling and function. Nat Rev Mol Cell Biol 16(1): 5-17.
44. Paik WK, Paik DC, Kim S (2007) Historical review: the field of protein methylation. Trends Biochem Sci 32(3): 146-52.
45. Bedford MT, Clarke SG (2009) Protein arginine methylation in mammals: who, what, and why. Mol Cell. 33(1): 1-13.
46. Yang XD, Lamb A, Chen LF (2009) Methylation, a new epigenetic mark for protein stability. Epigenetics. 4(7): 429-33.
47. Sharma BS (2018) Ultraviolet-Induced DNA Damage Promotes Methylation of the Cell-Cycle Checkpoint Kinase CHK1. Arch Cancer Res 6(2): 10.
48. Scott A, Song J, Ewing R, Wang Z (2014) Regulation of protein stability of DNA methyltransferase 1 by post-translational modifications. Acta Biochim Biophys Sin 46(3): 199-203.
49. Yu Z, Xiao Q, Zhao L, Ren J, Bai X, Sun M, et al. (2015) DNA methyltransferase 1/3a overexpression in sporadic breast cancer is associated with reduced expression of estrogen receptor-alpha/breast cancer susceptibility gene 1 and poor prognosis. Mol carcinog 54(9): 707-19.
50. Wang J, Hevi S, Kurash JK, Lei H, Gay F, Bajko J, et al. (2009) The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. Nat Genet 41(1): 125-129.
51. Ardito F, Giuliani M, Perrone D, Troiano G, Lo Muzio L (2017) The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy. Int J Mol Med 40(2): 271-280.
52. Du C, Zhang C, Hassan S, Biswas MH, Balaji KC (2010) Protein kinase D1 suppresses epithelial-to-mesenchymal transition through phosphorylation of snail. Cancer Res 70(20): 7810-7819.
53. Singh V, Ram M, Kumar R, Prasad R, Roy BK, Singh KK (2017) Phosphorylation: implications in cancer. Protein J 36(1): 1-6.
54. Cicenas J (2008) The potential role of Akt phosphorylation in human cancers. Int J Biol Markers 23(1): 1-9.
55. Shawver LK, Slamon D, Ullrich A (2002) Smart drugs: tyrosine kinase inhibitors in cancer therapy. Cancer cell 1(2): 117-123.
56. Roberts PJ, Der CJ (2007) Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 26(22): 3291.
57. Shields JM, Pruitt K, McFall A, Shaub A, Der CJ (2000) Understanding Ras: 'it ain't over'til it's over'. Trends Cell Biol 10(4): 147-54.
58. Blaydes JP, Luciani MG, Pospisilova S, Ball HM, Vojtesek B, Hupp TR (2001) Stoichiometric Phosphorylation of Human p53 at Ser315Stimulates p53-dependent Transcription. J Biol Chem 276(7): 4699-708.
59. Lilien J, Balsamo J, Arregui C, Xu G (2002) Turn-off, drop-out: functional state switching of cadherins. Dev Dyn 224(1): 18-29.
60. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1): 57-70.
61. Zuo L, Weger J, Yang Q, Goldstein AM, Tucker MA, Walker GJ, et al. (1996) Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat Genet 12(1): 97.
62. Datto MB, Hu PP, Kowalik TF, Yingling J, Wang XF (1997) The viral oncoprotein E1A blocks transforming growth factor beta-mediated induction of p21/WAF1/Cip1 and p15/INK4B. Mol Cell Biol 17(4): 2030-2037.
63. Melchior F, Schergaut M, Pichler A (2003) SUMO: ligases, isopeptidases and nuclear pores. Trends Biochem Sci 28(11): 612-618.

64. Seeler JS, Dejean A (2017) SUMO and the robustness of cancer. Nat Rev Cancer 17: 184–197.
65. Eifler K, Vertegaal AC (2015) SUMOylation-mediated regulation of cell cycle progression and cancer. Trends Biochem Sci 40(12): 779-793.
66. Morris JR, Boutell C, Keppler M, Densham R, Weekes D, Alamshah A, et al. (2009) The SUMO modification pathway is involved in the BRCA1 response to genotoxic stress. Nature 462(7275): 886-890.
67. Vlachostergios PJ, Papandreou CN (2012) The role of the small ubiquitin-related modifier (SUMO) pathway in prostate cancer. Biomolecules. 2(2): 240–255.
68. Hu L, Yang F, Lu L, Dai W (2017) Arsenic-induced sumoylation of Mus81 is involved in regulating genomic stability. Cell Cycle 16(8): 802–811.
69. Driscoll JJ, Pelluru D, Lefkimmiatis K, Fulciniti M, Prabhala RH, Greipp PR, et al. (2010) The sumoylation pathway is dysregulated in multiple myeloma and is associated with adverse patient outcome. Blood 115(14): 2827-2834.
70. Ivanschitz L, Takahashi Y, Jollivet F, Ayrault O, Le Bras M (2015) PML IV/ARF interaction enhances p53 SUMO-1 conjugation, activation, and senescence. Proc Natl Acad Sci U S A 112(46): 14278-14283.
71. Gallo LH, Ko J, Donoghue DJ (2017) The importance of regulatory ubiquitination in cancer and metastasis. Cell Cycle 16(7): 634-648.
72. Keutgens A, Zhang X, Shostak K, Robert I, Olivier S, Vanderplasschen A, et al. (2010) BCL-3 degradation involves its polyubiquitination through a FBW7-independent pathway and its binding to the proteasome subunit PSMB1. J Biol Chem 285(33): 25831-25840.
73. Nguyen LK, Kolch W, Kholodenko BN (2013) When ubiquitination meets phosphorylation: a systems biology perspective of EGFR/MAPK signalling. Cell Commun Signal 11(1): 52.
74. Magnani M, Crinelli R, Bianchi M, Antonelli A (2000) The ubiquitin-dependent proteolytic system and other potential targets for the modulation of nuclear factor-kB (NF-kB). Curr Drug Targets 1(4): 387-399.
75. Witowsky JA, Johnson GL (2003) Ubiquitylation of MEKK1 inhibits its phosphorylation of MKK1 and MKK4 and activation of the ERK1/2 and JNK pathways. J Biol Chem 278(3): 1403-1406.
76. Van Ree JH, Jeganathan KB, Malureanu L, Van Deursen JM (2010) Overexpression of the E2 ubiquitin–conjugating enzyme UbcH10 causes chromosome missegregation and tumor formation. J Cell Biol 188(1): 83-100.
77. Tzelepi V, Zhang J, Lu JF, Kleb B, Wu G, Wan X, et al. (2012) Modeling a lethal prostate cancer variant with small-cell carcinoma features. Clin Cancer Res 18(3): 666-677.
78. Wu X, Zhang W, Font-Burgada J, Palmer T, Hamil AS, Biswas SK, et al. (2014) Ubiquitin-conjugating enzyme Ubc13 controls breast cancer metastasis through a TAK1-p38 MAP kinase cascade. Proc Natl Acad Sci U S A 111(38): 13870-13875.
79. Kajiro M, Hirota R, Nakajima Y, Kawanowa K, So-ma K, Ito I, et al. (2009) The ubiquitin ligase CHIP acts as an upstream regulator of oncogenic pathways. Nat Cell Biol 11(3): 312.
80. Schwickart M, Huang X, Lill JR, Liu J, Ferrando R, French DM, et al. (2010) Deubiquitinase USP9X stabilizes MCL1 and promotes tumour cell survival. Nature 463(7277): 103-107.
81. Gu YY, Yang M, Zhao M, Luo Q, Yang L, Peng HM, et al. (2015) The de-ubiquitinase UCHL1 promotes gastric cancer metastasis via the Akt and Erk1/2 pathways. Tumour Biol 36(11): 8379-8387.
82. Iglesias-Gato D, Chuan YC, Jiang N, Svensson C, Bao J, Paul I, et al. (2015) OTUB1 de-ubiquitinating enzyme promotes prostate cancer cell invasion in vitro and tumorigenesis in vivo. Mol Cancer 14(1): 8.
83. Sharma P, Bhunia S, Poojary SS, et al. (2016) Global methylation profiling to identify epigenetic signature of gallbladder cancer and gallstone disease. Tumour Biol 37(11): 14687-14699.
84. Lemmon MA, Schlessinger J (2010) Cell signaling by receptor tyrosine kinases. Cell 141(7): 1117-34.
85. Grandal MV, Grovdal LM, Henriksen L, Andersen MH, Holst MR, Madshus IH, et al. (2012) Differential Roles of Grb 2 and AP-2 in p38 MAPK-and EGF-Induced EGFR Internalization. Traffic 13(4): 576-585.
86. Raju U, Riesterer O, Wang ZQ, Molkentine DP, Molkentine JM, Johnson FM, et al. (2012) Dasatinib, a multi-kinase inhibitor increased radiation sensitivity by interfering with nuclear localization of epidermal growth factor receptor and by blocking DNA repair pathways. Radiother Oncol 105(2): 241-249.
87. Zwang Y, Yarden Y (2006) p38 MAP kinase mediates stress-induced internalization of EGFR: implications for cancer chemotherapy. EMBO J 25(18): 4195-206.
88. Tong J, Taylor P, Moran MF (2014) Proteomic analysis of the epidermal growth factor receptor (EGFR) interactome and post-translational modifications associated with receptor endocytosis in response to EGF and stress. Mol Cell Proteomics 13(7): 1644-1658.

89. Frogne T, Laenkholm AV, Lyng MB, Henriksen KL, Lykkesfeldt AE (2009) Determination of HER2 phosphorylation at tyrosine 1221/1222 improves prediction of poor survival for breast cancer patients with hormone receptor-positive tumors. Breast Cancer Res 11(1): R11.
90. Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, Baselga J (2001) Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res 61(12): 4744-4749.
91. Gijsen M, King P, Perera T, Parker PJ, Harris AL, Larijani B, et al. (2010) HER2 phosphorylation is maintained by a PKB negative feedback loop in response to anti-HER2 herceptin in breast cancer. PLoS Biol 8(12): e1000563.
92. Chaturvedi P, Singh AP, Batra SK (2008) Structure, evolution, and biology of the MUC4 mucin. FASEB J 22(4): 966-981.
93. Hubalek M, Brunner C, Mattha K, Marth C (2010) Resistance to HER2-targeted therapy: mechanisms of trastuzumab resistance and possible strategies to overcome unresponsiveness to treatment. Wiener Med Wochenschr 160(19-20): 506-512.
94. Peiris D, Spector AF, Lomax-Browne H, Azimi T, Ramesh B, Loizidou M, et al. (2017) Cellular glycosylation affects Herceptin binding and sensitivity of breast cancer cells to doxorubicin and growth factors. Sci Rep 7: 43006.
95. Stowell SR, Ju T, Cummings RD (2015) Protein glycosylation in cancer. Annu Rev Pathol 10: 473-510.
96. Ju T, Wang Y, Aryal RP, Lehoux SD, Ding X, Kudelka MR, et al. (2013) T n and sialyl-Tn antigens, aberrant O-glycomics as human disease markers. Proteomics Clin Appl 7(9-10): 618-631.
97. Atsriku C, Britton DJ, Held JM, Schilling B, Scott GK, Gibson BW, et al. (2009) Systematic mapping of posttranslational modifications in human estrogen receptor-α with emphasis on novel phosphorylation sites. Mol Cell Proteomics 8(3): 467-480.
98. Miyoshi Y, Murase K, Saito M, Imamura M, Oh K (2010) Mechanisms of estrogen receptor-α upregulation in breast cancers. Med Mol Morphol 43(4): 193-196.
99. Hayashi SI, Yamaguchi Y (2008) Estrogen signaling pathway and hormonal therapy. Breast Cancer 15(4): 256-261.
100. Zhu J, Zhao C, Kharman-Biz A, Zhuang T, Jonsson P, Liang N, et al. (2014) The atypical ubiquitin ligase RNF31 stabilizes estrogen receptor α and modulates estrogen-stimulated breast cancer cell proliferation. Oncogene 33(34): 4340-4351.
101. Zhuang T, Zhu J, Li Z, Lorent J, Zhao C, Dahlman-Wright K, et al. (2015) p21-activated kinase group II small compound inhibitor GNE-2861 perturbs estrogen receptor alpha signaling and restores tamoxifen-sensitivity in breast cancer cells. Oncotarget 6(41): 43853-43868.
102. Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, et al. (2012) Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia 26(11): 2326-2335.

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