COMMENTARY

Pathological functions and therapeutic targets of post-translational modifications in pan-cancer

Ye Zhu,[1,2,3] Rongyang Xu,[1,2,3] Luyao Wang,[1,2,3] Guanglong Huang,[1,2,3] and Shanqiang Qu[1,2,3,*]

[1]Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

[2]The Laboratory for Precision Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

[3]The First Clinical Medical College of Southern Medical University, Guangzhou 510515, China

*Correspondence: qushq3@163.com

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A recent publication titled " Pan-cancer analysis of post-translational modifications reveals shared patterns of protein regulation" graced the pages of *Cell* on August 31, 2023 [1]. This groundbreaking study delves into a comprehensive examination of protein post-translational modifications (PTMs), harnessing a trove of multi-omics data obtained from 1110 patients across 11 distinct cancer classifications (Figure 1).[1] The authors adeptly identify both common and distinct patterns of protein regulation in diverse cancer types, shedding light on the intricate realm of protein PTMs. This study revealed potential new therapeutic pathways.[1] These findings highlight the potential of proteomics-driven precision medicine research to decipher carcinogenic drivers and their clinical applications, as well as the important value of PTMs in understanding carcinogenic mechanisms.

The vast diversity of PTMs, as well as their intricate crosstalk, is intricately connected to numerous pivotal signaling events that underpin neoplastic transformation, carcinogenesis, and metastasis.[2,3] Various PTMs play imperative pathological roles encompassing all facets of cancer hallmark functions, cancer metabolism, and regulation of the tumor microenvironment. Although previous studies have revealed some effects of PTMs on cancer,[2] our understanding of whether a common regulatory pattern exists for such modifications across multiple cancer types, as well as the interplay between different types of PTMs and the intricate regulatory network they collectively form, remains limited. Thus, delving into potential PTMs mechanisms within a pan-cancer framework assumes paramount significance. Unraveling the PTM-mediated processes that steer cancer development and progression, we can

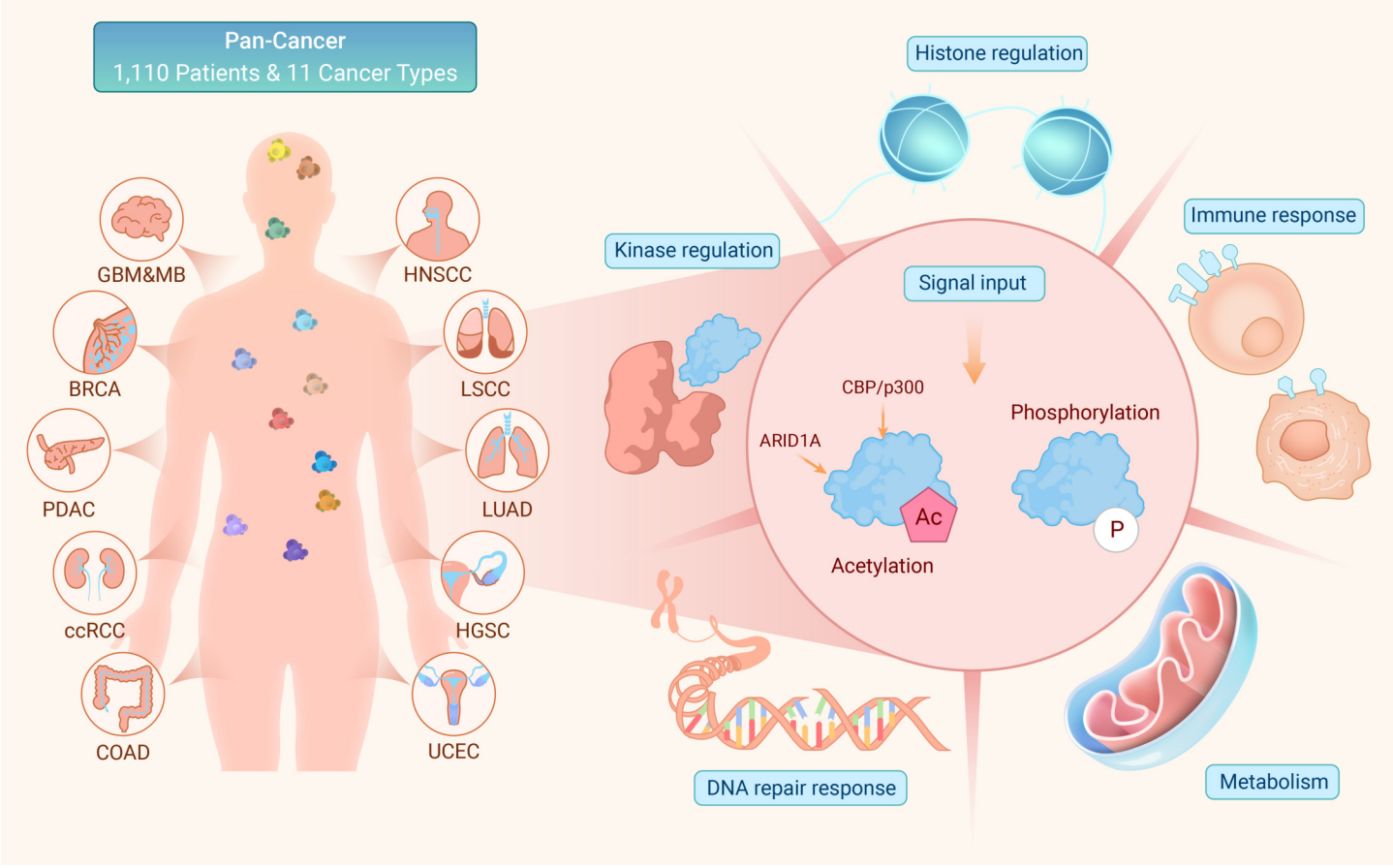

Figure 1. The shared pattern of post-translational modifications (PTMs) changes observed across over 1,000 patients spanning 11 diverse cancer types highlights the prominent role that PTMs play in these characteristic cancer processes Moreover, it unveils novel and promising therapeutic avenues for cancers.

potentially unearth novel therapeutic targets with the potential to revolutionize cancer treatment strategies.

To conduct comprehensive pan-cancer analyses encompassing shared genes, proteins, and patterns of PTMs among various cancers, the authors integrated data from the complete Clinical Proteomic Tumor Analysis Consortium (CPTAC) cohort, encompassing 1,110 patients across 11 cancer types. They detected an average of approximately 25,000 germline variants in the exome, as well as around 320 exonic somatic mutations per patient. Notably, the somatic mutation burden was carefully matched with the Cancer Genome Atlas cohort. Per patient, the study highlighted an average detection

of approximately 10,000 proteins, around 22,000 phosphorylation sites, and approximately 6,000 acetylation sites. Notably, the authors discovered a higher degree of shared transcriptomic and proteomic features among different cancer types. However, the PTMs features exhibited substantial variation across the various types of cancer. The study revealed a notable upregulation of 22 proteins phosphorylation sites in pan-cancer. Among the identified candidates, SRSF2, a splicing factor abundant in serine and arginine residues, emerged as a conspicuous standout. It was observed that the phosphorylated form of SRSF2 interacts with E2F1 to facilitate transcriptional regulation of cell cycle target genes. This interaction ultimately promotes the proliferation of lung cancer cell lines. Significant clusters of the protein ARID1A, a SWI/SNF chromatin remodeling factor that is frequently mutated in pan-cancer and exerts a multifaceted role in tumorigenesis, were exclusively observed within acetylated common proteins. Next, the authors identified PTMs-related features including dysregulation of DNA repair pathways driven by phosphorylation, metabolic regulation associated with immune response driven by acetylation and the regulation of specific kinases and histone impacted by the interplay between acetylation and phosphorylation.

In this study, the authors sought to elucidate the influence of PTMs regulation on this intricate interaction across different cancer types. Employing unsupervised clustering methods, the researchers identified four distinct immune subtypes that span multiple cancer types. Among these immune subtypes, the "hot" subtype exhibited heightened activation of immune-related pathways, accompanied by a marked presence of immunosuppressive markers. Within the "cool" subtype, noteworthy disparities in acetylation levels were observed in various metabolic pathways including propionate metabolism, oxidative phosphorylation, and fatty acid (FA) metabolism pathways. Acetylation, in these pathways, serves a crucial inhibitory function. In the "hot" subtype, a substantial prevalence of elevated phosphorylation sites was evident within the identical structural domain. Conversely, in the "cool" subtype, several proteins associated with fatty acid metabolism exhibited clusters of sites characterized by diminished acetylation levels.

Furthermore, the authors conducted an in-depth analysis of histone acetylation patterns. They observed that histone acetylation could be categorized into two distinct structural groups: group 1 (including H1, H3, and H4) and group 2 (including H2A and H2B). Interestingly, a substantial correlation was noted between the average acetylation profiles of pairs within the same structural group. To explore the connection between crucial regulatory factors and histone acetylation levels, the authors investigated the association between the protein abundance of the histone acetyltransferase CBP/p300 and various acetylation sites. Notably, multiple positive correlations were identified, particularly with acetylation sites on the N-terminal region of H2B, including K11, K15, K16, and K20. This discovery harmonizes with the substrate specificity exhibited by CBP/p300, known to exhibit a predilection for these precise acetylation sites. The study shifted its attention towards understanding how metabolic alterations in pan-cancer immune subtypes influence histone regulation. Notably, elevated FA metabolism was observed in immunologically "cold" tumors, along with reduced acetylation levels at specific histone acetylation sites (22/61 and 31/61) in comparison to immunologically "hot" tumors. This data also revealed a decrease in acetylation at site 22/61 relative to immunologically "hot" tumors and site 31/61 relative to immunologically "hot" tumors. Finally, to gain further insights into the potential interplay between adjacent histone phosphorylation and acetylation sites, the study undertook an analysis of their correlations. Among the 81 pairs of histone acetylation and phosphorylation sites examined, a significantly correlation was observed in 12 pairs. Additionally, the lysine PTMs selectivity of 207 recombinant Ser/Thr kinases was experimentally characterized, employing abbreviated peptide substrates. Interestingly, the authors noted a general preference among the kinase group for substrates containing acetylated lysine. Nonetheless, there were exceptions where specific kinases exhibited a preference for phosphorylation of adjacent serine or threonine residues when an acetylated lysine was present, as opposed to an unmodified lysine. Notably, the substrate motifs of AurB and PKACB displayed a propensity for selecting acetylated lysine in this particular context.

PTMs play a pivotal role in the regulation of signal transduction and are crucial for various cellular processes, including protein-protein interactions, stability of proteins, localization, and numerous other essential functions.[4] The current study presents a comprehensive analysis of pan-cancer patterns pertaining to protein acetylation and phosphorylation alterations in distinct cancer types. Through this analysis, the researchers shed light on the dynamic changes in PTMs that occur within signature cancers. The identified patterns provide insights into subpopulations of tumors across various cancer types. These subpopulations exhibit distinct characteristics, such as dysregulation of DNA repair driven by phosphorylation, metabolic alterations associated with immune response triggered by acetylation, and the impact of crosstalk between acetylation and phosphorylation on kinase specificity. Moreover, the study also highlights the importance of altered histone regulation. Collectively, these findings underscore the significant role of PTMs in the adaptive response of tumor cells to both intracellular and environmental changes. Gaining a more profound understanding of the regulatory processes involving PTMs that contribute to the development and progression of cancer holds tremendous potential. The identified patterns of PTMs in different cancers have a direct impact on therapeutic intervention and clinical decision making. By understanding these shared PTM patterns, potential therapeutic targets can be identified, leading to tailored treatment strategies and improved patient outcomes. These findings also offer opportunities for personalized medicine and the development of biomarkers for disease prognosis and treatment response. Ultimately, the integration of PTM analysis into clinical practice can optimize treatment strategies and contribute to advancing precision medicine in various cancer types. Moving forward, one proposed solution is the integration of cryo-TEM structures with mass-spectrometry and microscopic analysis to gain a comprehensive understanding of PTM roles in disease and physiology. Cryo-TEM offers high-resolution structural information, while mass-spectrometry identifies PTMs and microscopic analysis visualizes PTM-dependent molecular interactions. This combined approach holds promise for addressing the complexities of PTMs, improving our knowledge of their significance in diseases. There is a strong aspiration to expand the coverage of tumor types and increase the number of cases studied. Additionally, incorporating spatial genomics and enhanced proteomic approaches is envisioned to provide a more comprehensive and precise understanding of the molecular and cellular organization of tumors. These advancements aim to improve the clustering and analysis of underlying biological mechanisms. Furthermore, future endeavors aim to establish correlations between biological mechanisms, patient prognosis, and drug response, thereby bridging the gap between mechanistic understanding and functional outcomes.

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DECLARATION OF INTERESTS

The authors declare no competing interests.