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Proteomics-driven precision oncology: from molecular profiling to biomarker discovery

Yixuan Shi[1,2,†], Songting Yang[2,†], Yale Chen[2,†], Jiyun Chen[1] and Bingbing Hao[1,*]

[1] State Key Laboratory of Metabolic Dysregulation & Prevention and Treatment of Esophageal Cancer, Tianjian Laboratory of Advanced Biomedical Sciences, School of Convergence Medicine, Zhengzhou University, Zhengzhou 450052, China
[2] School of Basic Medical Sciences, College of Medicine, Zhengzhou University, Zhengzhou 450052, China

† These authors contributed equally to this work.

* Correspondence author; E-mail: bbhao@zzu.edu.cn.

Highlights:

- Advances in mass spectrometry (MS) enable scalable and high-resolution proteomics across bulk, single-cell, and spatial contexts.
- MS-based proteomics facilitates the discovery of cancer biomarkers.
- Artificial intelligence (AI)-assisted multi-omics integration accelerates clinical translation in precision oncology.

Abstract: Proteomics enables systematic, context-dependent characterization of the proteome, and has emerged as a cornerstone of precision cancer medicine. Although the systematical analysis of molecular profiling has transformed oncology over the past two decades, substantial heterogeneity in therapeutic responses still persists among patients with similar genetic alterations, highlighting the limitations of static genomic information. By directly interrogating signaling pathways and regulatory networks of proteins and post-translational modifications (PTMs) that drive tumor initiation, progression, and therapy resistance, proteomics bridges the gap between genomic alterations and phenotypic outcomes. Recent advances in mass spectrometry have enabled low-cost, high-throughput, and high-resolution proteomics from bulk to single cells, providing unprecedented insights into tumor heterogeneity. Integrative analysis of multi-omics, including genomics, transcriptomics and proteomics data, facilitates the construction of multidimensional molecular landscapes that reveal novel biomarkers and therapeutic targets. In this review, we summarize recent advances in proteomics-based biomarker discovery, highlight emerging single-cell and spatial proteomics technologies, and discuss future directions for integrating multi-omics, clinical information, and artificial intelligence to accelerate clinical translation.

Keywords: proteomics; single-cell proteomics; spatial proteomics; biomarker discovery; precision medicine

1. Introduction

Proteomics systematically characterizes the full complement of proteins, including their abundance, post-translational modifications, spatial organization, and interaction networks in a context-dependent manner [1–3]. In the two decades following the completion of the Human Genome Project, cancer therapy has undergone a fundamental paradigm shift, transitioning from treatment strategies dominated by histopathological classification toward precision oncology guided by molecular profiling [4,5] . Despite this progress, marked heterogeneity in therapeutic responses persists, even among patients harboring identical genetic alterations and treated with the same targeted agents. This inconsistency underscores the limitations of static genomic information and has redirected attention toward proteins, the dynamic functional effectors that ultimately govern cellular behavior.

By directly interrogating the signaling pathways and regulatory networks that drive tumor initiation progression, and therapeutic resistance, proteomics bridges the critical gap between genomic alterations and phenotypic outcomes, providing a functional framework for individualized cancer therapy.

Concurrent advances in mass spectrometry-based proteomics technologies have further propelled the field, enabling low cost, high-throughout, large-scale, high-resolution profiling of proteomes across thousands of tumor specimens, expending the scope of proteomics analyses from bulk to single cell revolved profiling, and enabling unprecedented insight into cellular and tumor heterogeneity [6]. When integrated with genomic and transcriptomic data, these approaches facilitate the construction of multidimensional, cross-cancer molecular landscapes, uncovering biomarkers, therapeutic targets, and mechanistic insights that remain inaccessible through genomics alone.

Proteomics-driven precision oncology has achieved substantial advances in mechanistic elucidation, biomarker discovery, and therapeutic development in cancer research. In this review, we summarize recent advances in proteomics-based biomarker discovery across various cancer types. By integrating multi-omics landscapes, we highlight clinically relevant biomarkers identified in various cancers. Furthermore, we emphasize the unique strengths of single-cell and spatial proteomics in elucidating biological functions and resolving tumor heterogeneity. We further discuss future directions centered on integrative multi-omics strategies that combine proteomics data with transcriptomic, epigenomic, metabolomic, and clinical phenotypic information. The incorporation of artificial intelligence and machine learning to high-dimensional datasets is expected to facilitate the development of predictive and clinically interpretable models, thereby accelerating biomarker translation into clinical practice. Collectively, proteomics-based multimodal integration and intelligent analytics represent critical drivers of next-generation precision oncology.

2. MS-based proteomics

Proteomics provides a powerful framework for elucidating the molecular mechanisms driving tumorigenesis and cancer progression by systematically characterizing the composition, abundance, and functional states of proteins in tumor cell [3].

Currently, bottom-up proteomics is the predominant strategy for large-scale protein analysis, relying on enzymatic digestion of complex protein mixtures into peptides that are subsequently identified and quantified by mass spectrometry. Within this framework, data-dependent acquisition (DDA) has traditionally served as the standard approach in this field, but its reproducibility and quantitative accuracy

are inherently constrained by the stochastic selection of precursor ions. Advances in quantification strategies have further expended the applicability of bottom-up proteomics. Isobaric labelling approaches, such as tandem mass tags (TMT), enable simultaneous quantification of over 30 samples in a single experiment, increasing analytical throughput while largely preserving proteome depth despite reduced instrument time per sample [7]. Nevertheless, TMT-workflow typically require extensive sample fractionation using high-performance liquid chromatography (HPLC) to reduce the complexity of samples, resulting in increased experimental time and cost. In parallel, continuous improvements in mass spectrometry sensitivity, scanning speed and data-interpretation software have facilitated the development of data-independent acquisition (DIA), an alternative strategy that systematically fragments all detectable precursor ions, especially in high-throughput studies [8]. Complementarily, label-free quantification based on DIA has become an indispensable tool for large-scale cohort analyses due to its low cost, lack of chemical modification requirements, and compatibility with diverse sample type, and it has demonstrated robust and reproducible performance in multiple benchmarking studies. Alongside advances in data acquisition, proteomics data analysis has increasingly shifted from traditional database-search-based toward deep learning-driven approaches. For instance, algorithms such as Prosit and CHIMERYS leverage machine learning to predict peptide fragmentation patterns or to uniformly analyze diverse data types. These methods substantially enhance peptide and protein identification rates while maintaining stringent false discovery rate (FDR) control [9]. In addition, DIA data-searching software tools, such as Spectronaut [10] and Data-independent acquisition by neural networks (DIA-NN) [11], enable accurate and deep proteome coverage under high-throughput conditions. Collectively, these technological and computational advances have optimized the quality and robustness of bottom-up proteomics, providing a solid foundation for multi-omics integration and extending applications to complex biological systems in both physiology and physiology [12].

3. Proteomics-based cancer biomarker discovery

Over the past decades, at the beginning of the proteogenomic studies of breast, colon and ovarian cancer with large-scale cohorts, a series of comprehensive landscape studies across multiple cancer types have been published. These studies have systematically characterized proteomics and post-translational modification (PTM) features, and through integrating genomics and transcriptomics, have elucidated disease pathogenesis, and identified potential cancer biomarkers and therapeutic targets for individual cancer type.

The discovery of biomarkers is central to advancing precision medicine, enabling early cancer screening, accurate diagnosis, prognosis assessment, and prediction of therapeutic response. Proteomics plays a critical role in tumor biomarker discovery due to unique capacity to simultaneously measure protein expression levels and posttranslational modification states across complex biological system [13]. In recent years, multi-omics integration strategies—combining genomics, transcriptomics, proteomics, and PTM omics—have substantially improve biomarker identification efficiency and biological relevance. Previous studies have reported mass spectrometry (MS)-based proteogenomics for precision ontology in cancer research [1,14]. Complementarily, we systematically summarized the biomarkers across 25 types of cancers based on the analysis of integrating MS-based proteogenomics datasets (Figure 1, Supplementary Table S1), which will expand our understanding for cancer precision oncology. Here, we highlight the biomarker discovery within three years by integrative analysis of proteomics with other multi-omics.

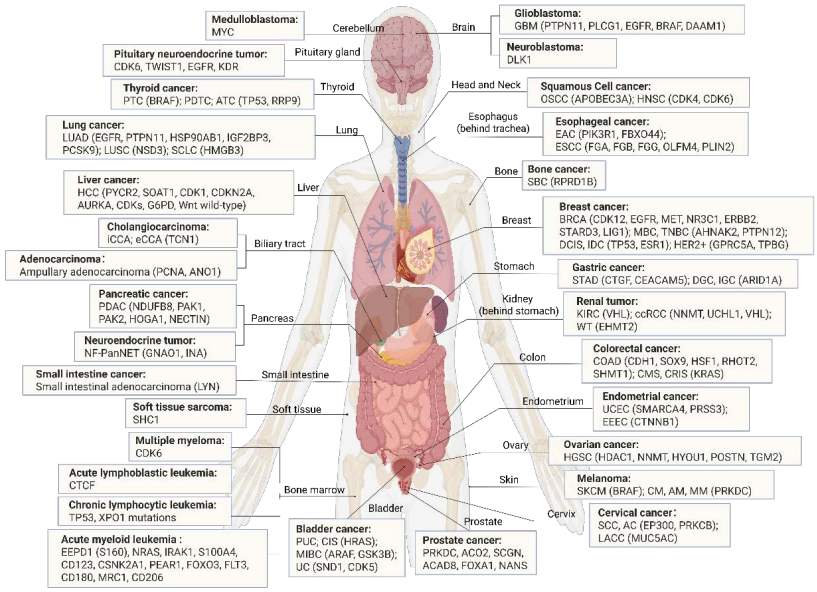

Figure 1. Proteomics-driven cancer biomarker discovery. Medulloblastoma [15]; pituitary neuroendocrine tumor [16]; thyroid cancer: PTC (papillary thyroid carcinoma) [17], PDTC (poorly differentiated thyroid carcinoma) and ATC (anaplastic thyroid carcinoma) [18]; lung cancer: LUAD (lung adenocarcinoma) [19–23], LUSC (lung squamous cell carcinoma) [24], and SCLC (small cell lung cancer) [25]; liver cancer: HCC (hepatocellular carcinoma) [26–30]; cholangiocarcinoma: iCCA (intrahepatic cholangiocarcinoma) and eCCA (extrahepatic cholangiocarcinoma) [31]; ampullary adenocarcinoma [32]; pancreatic cancer: PDAC (pancreatic ductal adenocarcinoma) [33–36]; neuroendocrine tumor: NF-PanNET (non-functional pancreatic neuroendocrine tumor) [37]; small intestinal cancer: small intestinal adenocarcinoma [38]; soft tissue sarcoma [39]; multiple myeloma [40]; acute lymphoblastic leukemia [41]; chronic lymphocytic leukemia [42]; acute myeloid leukemia [43–47]; bladder cancer: PUC (papillary urothelial carcinoma), CIS (carcinoma *in situ*) [48], MIBC (muscle-invasive bladder cancer) [49], and UC (urothelial carcinoma) [50]; glioblastoma [17,51–53]; neuroblastoma [54]; squamous cell carcinoma: OSCC (oral squamous cell carcinoma) [55] and HNSC (head and neck squamous cell carcinoma) [56]; esophageal cancer: EAC (esophageal adenocarcinoma) [57,58] and ESCC (esophageal squamous cell carcinoma) [59–61]; bone cancer: SBC (small blue cell tumor) [62]; breast cancer: BRCA (breast cancer susceptibility genes) [63–67], MBC (metastatic breast cancer), TNBC (triple-negative breast cancer) [68,69], DCIS (ductal carcinoma *in situ*), IDC (invasive ductal carcinoma) [70], and $HER2^{+}$ (human epidermal growth factor receptor 2-positive breast cancer) [71]; gastric cancer: STAD (stomach adenocarcinoma) [72,73], DGC (diffuse-type gastric cancer) and IGC (intestinal-type gastric cancer) [74]; renal tumor: KIRC (kidney renal clear cell carcinoma) [75], ccRCC (clear cell renal cell carcinoma) [76–78], and WT (wilms tumor) [79]; colorectal cancer: COAD (colon adenocarcinoma) [80–84], CMS (consensus molecular subtypes of colorectal cancer) and CRIS (colorectal cancer intrinsic subtypes) [85]; endometrial cancer: UCEC (uterine corpus endometrial carcinoma) [86,87] and EEEC (endometrial endometrioid carcinoma) [88]; ovarian cancer: HGSC (high-grade serous carcinoma) [89–93]; melanoma: SKCM (skin cutaneous melanoma) [94], CM (cutaneous melanoma), AM (acral melanoma), and MM (mucosal melanoma) [95]; cervical cancer: SCC (squamous cell carcinoma), AC (adenocarcinoma) [96], and LACC (locally advanced cervical cancer) [97]; prostate cancer [98–102].

Multi-omics analysis of 435 samples from 148 colorectal cancer (CRC) patients revealed stage-specific molecular alterations during tumor progression. KRAS proto-oncogene, GTPase/B-Raf proto-oncogene, serine/threonine kinase (KRAS/BRAF) mutations and elevated oxidative phosphorylation characterized the intraepithelial neoplasia stage, while chr17q loss, chr20q gain, and tumor protein p53 (TP53) mutations drove later progression and tumor microenvironment remodeling. Subtype and location analyses identified distinct progression paths and ankyrin repeat domain-containing protein 22 (ANKRD22)-driven glycolysis in right-sided CRC, with DEAD-box helicase 5 (DDX5) loss promoting tumorigenesis in a mouse model [85]. Comprehensive proteomics and proteogenomic analyses elucidated the molecular basis of metastasis and therapy resistance in colorectal cancer. In early-stage disease, proteomics profiling of formalin-fixed paraffin-embedded (FFPE) samples from 221 patients with T1 CRC identified lymph node metastasis (LNM)-associated molecular alterations and enabled the development of accurate predictive models, including a machine-learning-based 55-protein classifier, a simplified nine-protein panel, and a five-protein immunohistochemistry (IHC) model. Functional assays demonstrated that Ras homolog family member T2 (RHOT2) suppresses early metastatic potential by inhibiting cancer cell migration and invasion [84]. In advanced disease, integrated proteogenomic analysis of 102 samples from 34 treatment-naïve colorectal liver metastasis (CRLM) patients revealed profound metabolic reprogramming, particularly in carbon metabolism. Serine hydroxymethyltransferase 1 (SHMT1)-driven one-carbon metabolism promoted metastasis via formate-mediated AMP-activated protein kinase (AMPK) inhibition, while Proviral integration site for Moloney murine leukemia virus kinase (PIM)-dependent N-myc downstream regulated gene 1 (NDRG1) Ser330 phosphorylation enhanced liver metastasis through ubiquitin-mediated degradation. Two proteomics CRLM subtypes with distinct prognoses were identified, and formiminotransferase cyclodeaminase (FTCD), glycerol-3-phosphate dehydrogenase 1 (GPD1), superoxide dismutase 2 (SOD2), and eukaryotic translation initiation factor 4B (EIF4B) Ser422 phosphorylation were validated as prognostic biomarkers [83]. Furthermore, proteomics profiling of 254 CRC tumors defined four molecular subtypes with distinct therapeutic responses, closely linked to immune regulatory pathways. Mechanistically, heat shock transcription factor 1 (HSF1) conferred radiotherapy resistance through enhanced DNA repair and cell-cycle progression, whereas elevated histone deacetylase 6 (HDAC6) expression mediated cetuximab resistance. Predictive proteomics-based models were validated by protamine (PRM), providing clinically actionable insights into metastasis risk and treatment resistance in CRC [82].

Duodenal cancer (DC) shows marked subtype heterogeneity and poorly defined carcinogenesis. Proteogenomic analysis of 438 samples from 156 patients revealed that chr8q gain-driven LYN proto-oncogene, Src family tyrosine kinase (LYN) amplification promotes progression via mitogen-activated protein kinase (MAPK) signaling, while dystonin (DST) mutations activate mechanistic target of rapamycin kinase (mTOR) in adenocarcinoma. Proteome-based analyses defined stage-specific trajectories and oncogenic waves across DC subtypes. The druggable enzyme alanyl-tRNA synthetase 1 (AARS1) was upregulated in tumors with high mutation burden and immune infiltration and promoted tumorigenesis by suppressing apoptosis, highlighting potential therapeutic targets [38].

Comprehensive proteogenomic analyses reveal the molecular heterogeneity and therapeutic vulnerabilities of lung cancer. In LUAD presenting as subsolid nodules, early cholesterol metabolism dysregulation and PCSK9 loss drive tumor initiation, while sustained ER stress marks malignant progression [20]. A large-scale LUAD proteogenomic study further highlighted driver mutations,

chromosomal instability, and exposure-related processes, providing biomarkers and subtype-specific targets to advance precision lung cancer therapy [22]. In SCLC, FAT atypical cadherin 1 (FAT1) mutation, RB transcriptional corepressor 1 (RB1) deletion, and chromosome 5q loss promote tumorigenesis, with high mobility group box 3 (HMGB3) and caspase 10 (CASP10) as prognostic markers and immune suppression linked to zinc finger homeobox 3 (ZFHX3) mutations; four subtypes with distinct therapeutic sensitivities were defined [25]. Across non-small cell lung cancer (NSCLC), five molecular subtypes beyond histology were identified, including a phosphatidylinositol 3-kinase-Akt signaling pathway (PI3K-Akt)-activated subtype with high metastatic potential.

Integrated proteogenomic analyses define the molecular evolution, subtypes, and therapeutic vulnerabilities of esophageal cancers. In ESCC, stage-resolved multi-omics profiling revealed key drivers of progression, including chromosome 3q gain in early lesions, TP53 mutations enhancing DNA replication, and mutations in A-kinase anchoring protein 9 (AKAP9), also known as MBD1-containing chromatin-associated factor 1 (MCAF1), activating glycolysis and Wnt signaling in advanced disease [60]. Distinct molecular tracks and poor-prognosis subtypes were identified, with lipid metabolism-driven immune suppression and hyperphosphorylated phosphoglycerate kinase 1 (PGK1) (S203) emerging as therapeutic targets [60,61]. Proteomics analyses further uncovered chromosomal alterations linked to prognosis, metastasis, and immune states, and identified robust biomarkers predictive of anti-programmed cell death protein 1 (PD-1) immunotherapy response [59]. In adenocarcinoma of the esophagogastric junction, integrated multi-omics profiling defined three molecular subtypes with distinct signaling, microenvironmental features, and druggable targets, including F-box protein 44 (FBXO44), providing a framework for precision therapy in esophageal cancers [58].

Proteogenomic studies have clarified key mechanisms of therapy response and progression in breast cancer. In TNBC, loss of protein tyrosine phosphatase non-receptor type 12 (PTPN12) induces mitotic stres, leading to chromosomal instability and increased sensitivity to taxane chemotherapy [69]. In estrogen receptor-positive (ER^+) breast cancer, neurofibromin 1 (NF1) depletion activates Rat sarcoma virus oncogene (RAS) and ER signaling, conferring sensitivity to combined mitogen-activated protein kinase kinase (MEK) inhibition and ER degradation, with proteomics supporting NF1 loss as a predictive biomarker [103]. Additionally, multi-omics analysis of breast ductal carcinoma revealed a stepwise progression from benign lesions to invasive disease, identifying TP53-estrogen receptor 1 (ESR1)-driven early transition, nuclear receptor subfamily 3 group C member 1 (NR3C1)-mediated immune evasion in DCIS, and a T-cell lymphoma invasion and metastasis 1 (TIAM1)-androgen receptor (AR)-aldo-keto reductase family 1 member C1 (AKR1C1) axis promoting invasion, with AKR1C1 as a potential therapeutic target [70].

Comprehensive multi-omics analyses of primary and metastatic HCC revealed early, polyclonal dissemination, high genomic divergence, and pronounced neoantigen heterogeneity in metastases that impairs T-cell immunity. Somatic copy number alterations drive metastasis, while Wnt-wild-type subclones show enhanced metastatic fitness, activated fibroblast-rich microenvironments, and immunosuppressive B cells that exhaust cluster of differentiation 8-positive ($CD8^+$) T cells via the human leukocyte antigen E-natural killer group 2 member A (HLA-E-NKG2A) axis [28]. Complementing patient tumors, a liver cancer organoid biobank profiled by multi-omics defined prognostic proliferation and metabolism subtypes with distinct drug sensitivities. Integrative pharmaco-proteogenomics identified

biomarkers, effective drug combinations, and mTOR inhibition as a strategy to overcome lenvatinib resistance, providing a resource for functional precision medicine in liver cancer [104].

In addition to these cancer types, proteomics-based multi-omics integration has been extensively applied to a broad range of malignancies, including bladder cancer [48–50], ampullary adenocarcinoma [32], thyroid cancer [17,18], pancreatic neuroendocrine neoplasm [16], cervical cancer [96,97], skull-base chordoma [62], melanoma [95], soft tissue sarcoma [39], glioblastoma [51,52,105], clear cell renal cell carcinoma [77,78], cholangiocarcinoma [31,106], and ovarian cancer [93], thereby systematically elucidating tumor-specific molecular subtypes, signaling pathway dysregulation, metabolic reprogramming, tumor microenvironment heterogeneity, and clinically actionable therapeutic vulnerabilities, and collectively deepening our understanding of cancer initiation, progression, and treatment response.

Protein post-translational modifications play central regulators of regulating protein activity, stability, localization and interactions, and their dysregulation represents a major driving force in tumorigenesis. Aberrant expression or activation of PTM-regulating enzymes, such as kinases downstream of KRAS, epidermal growth factor receptor (EGFR), and BRAF, promotes uncontrolled cancer cell proliferation and survival. Many of these enzymes have become successful clinical drug targets, exemplified by kinase inhibitors [107–111]. The approval of first kinase inhibitor, imatinib, targeting the BCR-ABL fusion protein for chronic myeloid leukemia (CML) by Food and Drug Administration (FDA) in 2001 marks the beginning of precision oncology era [112].

To date, extensive studies have documented widespread alterations in PTMs, including phosphorylation, ubiquitination, acetylation, and glycosylation, across diverse cancer types with many PTM events as tumor drivers or diagnostic biomarkers. By enabling large-scale, high-throughput quantification of PTM sites, PTM-omics allows systematic mapping signaling pathways regulated by medicated proteins that are activated or suppressed under specific pathological conditions, such as hypoxia or drug resistance.

Among these approaches, phosphoproteomics has emerged as a core strategy for characterized tumor signaling landscapes and identifying therapeutic targets. For instance, in melanoma cells, phosphoproteomics profiling revealed extensive signaling alterations in DNA damage pathways following MEK and PI3K inhibitor treatment, providing mechanic insights into drug sensitivity and the rationale for combination therapies [113]. Similarly, in high-grade serous ovarian cancer (HGSOC), integrative proteogenomics analysis of enriched tumor epithelial cells identified differentially homologous recombination deficiency (HRD) network and differentially expressed proteins, laying the foundation for developing precision therapies targeting HRD or homologous recombination proficient (HRP) tumors [114]. Studies of hepatic progenitor cells indicated that tumor necrosis factor-like weak inducer of apoptosis (TWEAK) signaling induces inhibitor of DNA binding 1 (ID1) expression and activates multiple oncogenic pathways, including PI3K-Akt, MAPK, and HIF, driving a malignant phenotype [115].

Integration of phosphoproteomics with other multiomics provides a systematic framework for identifying clinically PTM biomarkers within complex molecular interaction networks. In glioblastoma (GBM), phosphorylation of protein tyrosine phosphatase non-receptor type 11 (PTPN11) and phospholipase C gamma 1 (PLCG1) has been identified as key molecular switches mediating oncogenic pathway activation [53]. In high-risk prostate cancer, phosphoproteomics analysis revealed the crucial role for forkhead box A1 (FOXA1) Ser331 phosphorylation in tumor progression [116]. Combined proteomics and phosphoproteomics profiling identified EIF4B Ser422 phosphorylation as subtype prognostic biomarkers in patients with colorectal liver metastasis [83].

Beyond phosphorylation, other types of PTMs also play important roles in tumorigenesis. For instance, integrated proteogenomics studies demonstrated that the acetyltransferase E1A binding protein p300 (EP300) enhance the acetylation of FOS-like antigen 2 (FOSL2) K222, promoting the malignant proliferation of cervical cancer [96]. Collectively, these findings underscore the pivotal role of PTMs in cancer biology and highlight their translational potential as biomarkers and therapeutic targets.

Recently, a comprehensive pan-cancer study integrated proteomics, phosphoproteomics, acetylomics, and genomics data from 1110 patients spanning 11 cancer types, with a particular focus on phosphorylation and acetylation [117]. This analysis identified 33 robust pan-cancer multi-omics signatures and revealed conserved regulatory principles of PTMs across malignancies. Aberrant phosphorylation was closely associated with defects in DNA damage repair pathways, with hypoxia modulating phosphorylation activity in homologous recombination-deficient tumors, while mismatch repair-deficient tumors exhibited reduced MRE11-RAD50-NBS1 complex (MRN) expression due to RAD50microsatellite alterations. Moreover, acetylation patterns of metabolic proteins stratified tumors into four immune subtypes and correlated with immune suppression and tumor proliferation. Importantly, extensive crosstalk between acetylation and phosphorylation was uncovered, exemplified by remodeling and spacing factor 1 (RSF1) acetylation inhibiting cyclin-dependent kinase 1 (CDK1)-mediated phosphorylation [117]. Despite limitations inherent to bulk tumor analyses, this work provides a valuable framework for PTM-informed precision oncology.

Complementing these finding, a pan-cancer proteogenimics studies integrating genomics, proteomics, and signaling features from 1056 tumor samples spanning 10 cancer types identifies seven distinct immune subtypes [118]. Notably, specific DNA alterations were associated with immune subtype identity and exerted measurable effects on proteomics landscapes. Analysis of kinase activity revealed subtype-specific signaling programs, highlighting potential therapeutic vulnerabilities. Integration of digital pathology further uncovered distinct patterns of immune and stromal cell infiltration corresponding to each immune subtype. The authors additionally examined associations between immune subtypes and clinical variables, including patient demographics and treatment responses, and assessed how genomic aberrations shape immune phenotypes [118]. Together, these findings provide a comprehensive proteogenomic framework for immune stratification across cancers and offer valuable insights for the rational design of immunotherapy and precision-targeted strategies.

4. Single-cell and spatial proteomics

Cells are inherently heterogeneous functional units. In complex biological systems, including developing tissues, organs and tumors, cellular composition is never uniform but instead forms dynamic ecosystems composed of diverse cell types and functional states [119]. As the ultimate executors of cellular function, proteins, through their abundance, modifications (e.g., phosphorylation), and activity states, directly govern cellular phenotype, signal transduction, and functional output [120]. Importantly, proteome is highly dynamic rather than static. Protein synthesis and degradation rates, collectively known as protein turnover, enable cells to rapidly adapt to microenvironment, undergo state transitions, and maintain functional plasticity. Consequently, resolving differences in protein abundance, modification, and turnover across distinct cellular subpopulations is essential for understanding dynamic phenotypes such as cellular stress responses, cell fate decisions, and the emergence of drug resistance. Although technical limitations have historically impeded systematic interrogation of these processes at single-cell

resolution [121], defining cell identity and functional diversity through cell-specific proteomics state, including their dynamic features, have become a central motivation and conceptual foundation for the development of single-cell proteomics (SCP) [122,123].

Tumors exemplify extreme cellular heterogeneity. Within individual tumor, cancer cells, immune cells and other distinct cell types coexist alongside a diverse tumor microenvironment. Aberrant protein signaling pathways, such as growth factor receptors and dysregulated phosphorylation networks, are key drivers of tumor growth, invasion, metastasis and tumor-resistance, and their activity often varies markedly among cellular subpopulations [119,120]. Traditional bulk proteomics analyses obscure these critical subpopulations by averaging signals across heterogeneous cell mixtures, thereby masking the molecular mechanisms underlying tumorigenesis and tumor resistance. While single-cell genomics and transcriptomics have provided valuable maps of cellular diversity [119], recent advances in spatially resolved transcriptomics have further highlight the importance of preserving tumor heterogeneity [124]. Nevertheless, because messenger RNA (mRNA) abundance does not reliably reflect protein level and modification states, directly measurement of the proteome at single-cell resolution is essential for a functional understanding of cellular behavior transcriptomics profiles alone cannot capture functional protein states [123,125]. Thus, deciphering this cell-type-specific protein expression is crucial for understanding disease progression and overcoming therapeutic resistance [122,123].

The conceptual and technological breakthrough in SCP have been driven. However, an individual cell contains only approximately 50-300 pg of total protein, making protein identification at the single cell extremely challenging [126]. With the development of high speed and sensitivity mass spectrometry, MS-based single-cell proteomics methods enable unbiased, discovery-driven identification and quantification of proteins, providing unparalleled access to functional proteomics landscape and unknown biology [125,127]. Continuous technological innovation is expanding the depth, throughput, and robustness of SCP analyses [122]. To date, improvement in sample preparation, mass spectrometry instrumentation and computational analysis has enabled MS-based single-cell proteomics to identify more than 5000 proteins from a single cell, providing unprecedented opportunities to comprehensively decode cellular complexity in both physiological and pathological contexts.

5. Single-cell proteomics

The rapid advancement of single-cell proteomics fundamentally relies on a series of groundbreaking technological innovations. These technologies are specifically designed to overcome the analytical challenges imposed by the extremely low protein content of individual cells (Figure 2A).

Miniaturized sample preparation represents the first major technological breakthrough. The primary challenge in single-cell proteomics analysis lies in achieving efficient, low-loss sample preparation. To address this, a variety of miniaturized techniques has been developed. Technologies such as nanodroplet processing in one pot for trace samples (nanoPOTS) [128] and nanodroplet processing in one pot for single cells (nPOP) [129] perform cell lysis, reduction, alkylation, and digestion in nanoliter-scale reactors, minimizing sample loss and enabling high-throughput parallel processing [130]. The Chip-Tip workflow coupled with 96-well plate enables nanoliter-scale, parallel preparation of up to 96 individual sample and is compatible with the Evosep One LC system, allowing streamlined, pipette-free sample transfer. Additional one-pot methods, employing diverse single cell isolation and lysis workflow, further broaden the sample preparation strategies for single cell proteomics [131].

Enhancing sensitivity at the liquid chromatography-mass spectrometry (LC-MS) interface is essential for single-cell analysis. State-of-the-art SCP leverages ultra-sensitive LC systems combined with advanced mass spectrometers, including narrow-bore columns to improve ionization efficiency [132] and Field Asymmetric Ion Mobility Spectrometry (FAIMS) interfaces coupled to high-resolution Orbitrap instruments to increase protein coverage within short gradients [133]. In particular, trapped ion mobility spectrometry (TIMS)-quadrupole time-of-flight (QTOF) mass spectrometers offer distinct advantages, improving scan speed and ion utilization, and enabling deeper proteome coverage and more accurate quantification at the single-cell level [130,134,135]. The addition of an ion mobility dimension further reduces the chemical complexity, thereby enhance of single-cell samples and improving quantitative accuracy.

To improve analytical throughput, multiplexing approaches are widely adopted in SCP workflow. Tandem mass tags labeling, particularly with higher-plex tandem mass tag pro reagents (TMTpro) reagents, allows multiple single-cell samples to be pooled and analyzed simultaneously, minimizing run-to-run variability and enabling precise relative quantification [130]. Building upon TMT-based multiplexing, the single-cell proteomics by mass spectrometry (SCoPE-MS) workflow and its iterations have established key paradigms for robust and reproducible single-cell quantification [136,137]. In addition, next-generation strategies, such as plexDIA combine data-independent acquisition with multiplex designs, enabling simultaneous analysis of multiple samples in a single experiment without expensive isotopic labels. These provides a cost-effective and scalable solution for large-scale SCP studies [130,134,138]. Collectively, these methods substantially improve the throughput, serving as foundational technologies propelling SCP forward. Notably, interference from carrier-derived peptides, arising from excessive carrier load, lysis buffer, or cross channel contamination, remains a major challenge. Therefore, defining and controlling the optimal carrier-to single-cell ratio is critical for further method optimization and accurate single-cell proteome measurement [139]. Additionally, the development of automated workflows, such as nanowell arrays, aims precisely to meet the demand for reproducible, high-throughput sample preparation [128].

Single-cell proteomics data are characterized by high noise, substantial missing values, and analytical complexity due to the extremely low protein content of individual cells, posing significant challenges for downstream analysis. Consequently, advanced computational and bioinformatics tools are essential to extract meaningful biological insights. Data preprocessing primarily aims to improve the signal-to-noise ratio through noise filtering, statistical correction, and missing-value imputation using algorithms such as K-nearest neighbors (KNN), random forest [130,134,140]. Peptide-to-protein inference presents an additional challenge at single-cell resolution, requiring stringent statistical models for accurate protein assignment.

Following preprocessing, unsupervised learning approaches including dimensionality reduction (principal component analysis (PCA), t-distributed stochastic neighbor embedding (t-SNE), uniform manifold approximation and projection (UMAP)) and clustering algorithms are widely applied to visualize data structure, classify cells, and identify novel cellular states or subtypes [130,141]. To link proteomics variation to cellular function, cross-omics integration is critical. Computational frameworks that integrate SCP with transcriptomic and genomic data enable the reconstruction of regulatory relationships and the identification of key functional nodes. Finally, pathway and enrichment analyses

map protein expression changes to biological processes, providing functional interpretation and a systems-level understanding of cellular heterogeneity.

Recently, robust and reproducible methods for single-cell proteomics were successfully applied to a wide range of biological and functional studies. Building upon the ability to generate high-resolution static snapshots, the field is now advancing toward capture the dynamic movie of the proteome at single-cell resolution. In 2025, Sabatier *et al.* reported a landmark technique termed single-cell pulsed stable isotope labeling (SC-pSILAC) [121]. This approach integrates a metabolic labeling with an ultra-sensitive single-cell mass spectrometry platform, enabling for the first time the high-throughput, parallel measurement of synthesis and degradation rates for thousands of proteins in individual cells. This breakthrough allows directly observation of how single cells reprogram their protein turnover networks in response to external stimuli, during fate decisions, or in the development of therapeutic resistance. As a result, functional proteomics is expended from what is expressed to how proteins dynamically turn over, providing an unprecedented dynamic perspective for investigating tumor heterogeneity and cellular plasticity at single-cell resolution. In parallel, SCoPE workflow was been applied to map early human blood cell differentiation [142], and to demonstrated that fertilization triggers early proteomics symmetry breaking in mammalian embryos [143]. These studies highlight that power of single-cell proteomics to elucidate dynamic protein regulation during developmental processes, demonstrating its broad applicability in uncovering fundamental biological principles in physiology and pathology at an unprecedented level of resolution.

Single-cell proteomics provides a powerful framework for dissecting immune cell activation and signaling heterogeneity by directly capturing protein abundance and signaling states that are not fully reflected at the transcriptomics level. An authoritative review further emphasized the core value of high-dimensional single-cell technologies, particularly those capable of detecting proteins and their modifications in cancer immunotherapy research. Such approaches enable detailed characterization of dynamic T cell exhaustion, immune checkpoint proteins, and the polarization states of myeloid cells, thereby providing functional insights into mechanisms underlying immunotherapy resistance [144]. By enabling longitudinal and multimodal profiling of circulating immune cells at single-cell resolution, this technology allows systematic dissection of the dynamic immune responses of peripheral blood mononuclear cells (PBMCs) in patients with acute-on-chronic liver failure (ACLF). Such high-resolution characterization deepens our understanding of immune dysregulation and opens new avenues for the development of precision immunotherapeutic strategies [145]. Analysis of the single-cell proteomics data enabled the detection of over 1100 proteins from individual tumor-associated neutrophils, providing a detailed characterization of neutrophil subsets in glioblastoma [146]. Looking ahead, the integration of single-cell multi-omics for high-resolution lineage tracing is expected to enable systematic mapping of dynamic changes across all cell types across the tumor ecosystem. Such integrative approaches hold promise for uncovering the cellular origins of drug resistance and predicting tumor evolutionary trajectories under therapeutic pressure, ultimately supporting truly individualized and proactive precision therapy, and delivering the right therapy to the right cell population at the right time [147].

In the field of integrated single-cell transcriptomics and proteomics analysis, combining these complementary omics layers has become a key strategy for establishing direct genotype-phenotype linkages and overcoming the limitations of each technology at single-cell resolution. A representation

example is the single-cell proteomics by mass spectrometry 2 (SCoPE2) protocol, which combined highly sensitive single-cell mass spectrometry-based proteomics and single-cell RNA sequencing (scRNA-seq) on samples derived from the same cell suspension [142]. Computational integration of these datasets enables direct comparison of mRNA abundance with corresponding protein expression at single-cell resolution. This approach revealed widespread decoupling between transcription and translation for many genes in macrophages and allowed more precise delineation of functionally distinct macrophage subpopulations, highlighting the unique contribution of proteomics measurements in defining cellular identity [137].

In summary, the technological ecosystem of single-cell proteomics is maturing through synergistic innovations across multiple dimensions: the miniaturization of sample preparation, the extreme sensitivity of mass spectrometry platforms, the multiplexing of labeling strategies, automatic equipment, and computational and bioinformatic frameworks. Together, these advances provide a powerful toolkit for systematically revealing both the static and dynamic aspects of protein function at single-cell resolution in tumor microenvironment for precision oncology.

6. Spatial proteomics

Although single-cell proteomics enables the characteristics of dynamic proteome changes, the discrimination of cellular subtypes, and provides deep insights into tumor heterogeneity, it generally lacks spatial context, thereby limiting the ability to elucidate the organization and interactions within tumor microenvironment. Spatial proteomics overcomes this limitation by systematically mapping the spatial distribution of proteins in FFPE or fresh-frozen tissue sections, offering critical insights into tissue architecture and cell-cell interactions within tumor (Figure 2B).

Recent advances in spatial proteomics technologies have further expanded analytical resolution and depth. Deep Visual Proteomics represents a prime example of this emerging direction [148]. In this approach, tissue section is first subjected to high-content microscopy imaging, allowing individual cells or regions of interest to be identified based on morphology or molecular markers. These selected cells are then isolated via automated laser capture microdissection and then analyzed using high-sensitivity mass spectrometry, enabling label-free, untargeted mapping of hundreds of proteins and providing a powerful platform for discovering novel spatial markers [148]. In addition, spatial proteomics strategies based on tissue expansion combined with mass spectrometry have demonstrated the capability to resolve subcellular proteomics while maintaining compatibility with archived clinical FFPE samples [149]. Complementary immunohistochemistry-based spatial proteomics methods, including cyclic immunofluorescence (cycIF), co-detection by indexing (CODEX), iterative bleaching extends multiplexity (IBEX), multiplexed ion beam imaging (MIBI) and imaging mass cytometry (IMC), enable highly multiplexed visualization of protein composition and spatial organization within tissues and tumors [150]. Furthermore, microscopy-guided proteomics, streamline workflows which integrate microscopy-based pattern generation, photolabeling, protein enrichment and subsequent MS analysis, have been applied to uncover protein constituents with specific subcellular structure in fixed cells and tissue biospecimens.

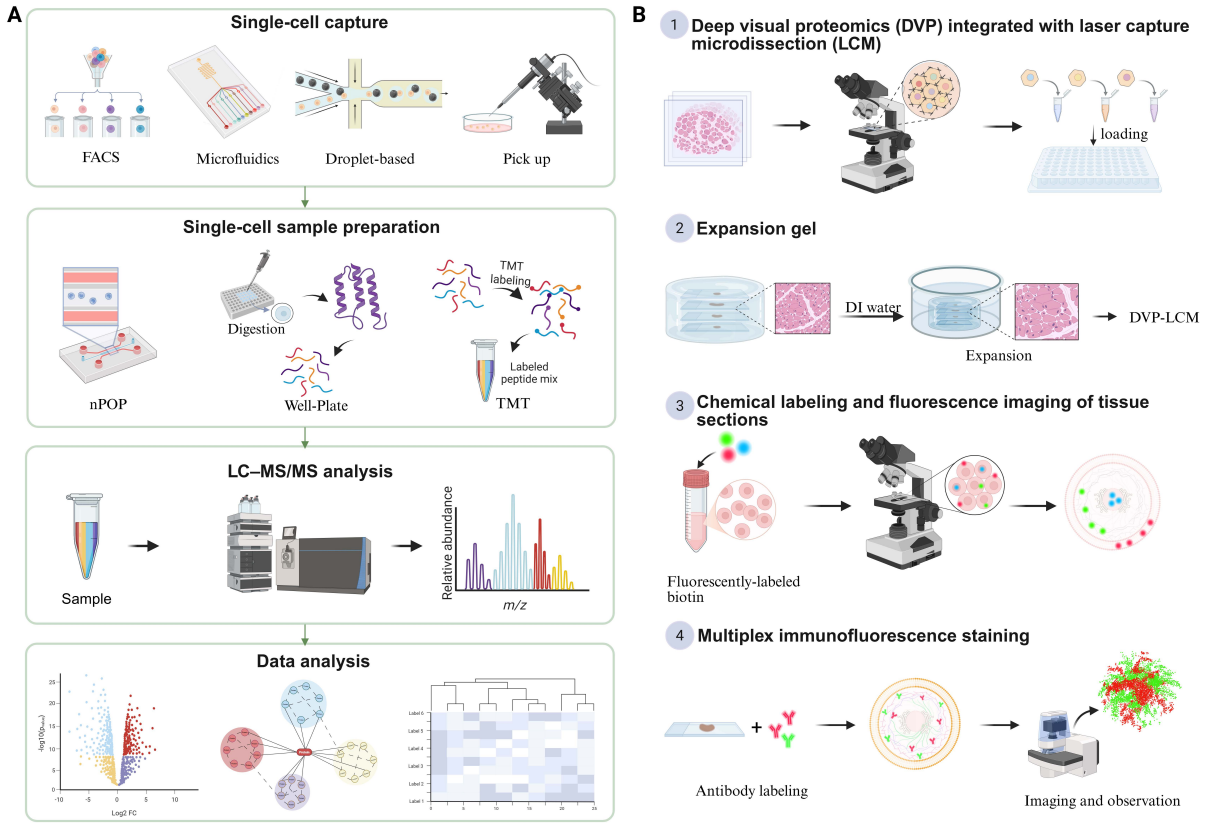

Figure 2. single-cell and spatial proteomics technologies. **(A)** Overview of single-cell proteomics workflows. Individual cells are isolated using fluorescence-activated cell sorting (FACS), microfluidic platforms, droplet-based encapsulation, or manual micromanipulation. Isolated cells undergo miniaturized sample preparation using platforms such as nanoPOTS (nanodroplet processing in one pot) or nPOP in low-volume multiwell formats. Proteins are enzymatically digested and labeled with tandem mass tags for multiplexed quantification. Peptide samples are analyzed by LC-MS/MS employing advanced acquisition strategies. Downstream computational analysis includes differential protein expression, clustering, and pathway enrichment to resolve cellular heterogeneity. **(B)** Spatially resolved proteomics approaches. Deep visual proteomics (DVP) integrates high-resolution microscopy with laser capture microdissection (LCM) to selectively isolate morphologically defined cells from tissue sections for downstream mass spectrometry analysis. Expansion microscopy physically enlarges tissue samples to enhance spatial resolution prior to microdissection. Complementary strategies such as chemical pan-protein labeling and multiplex immunofluorescence (mIF) staining enable visualization of protein distribution and tissue architecture before proteomics profiling.

Overall, CycIF, CODEX, and IBEX offer single-cell resolution and high multiplexing capacity, enabling detailed cellular phenotyping and spatial atlas construction. However, their reliance on predefined antibody panels limits unbiased proteome coverage and may introduce variability and batch effects across samples. In contrast, MIBI and IMC employ metal-based mass spectrometric detection to enhance signal stability and quantitative reproducibility, providing greater technical robustness in complex tissues—particularly within tumor microenvironments—yet they remain targeted approaches with restricted proteome depth. Deep Visual Proteomics, by comparison, enables broader proteomic

coverage within spatially defined regions and is better suited for mechanistic and discovery-driven studies. Nevertheless, DVP is limited by lower throughput, higher cost, and greater computational demands, with inherent trade-offs between spatial resolution and workflow complexity [151–153]. Collectively, imaging-based platforms prioritize high-dimensional spatial phenotyping and cellular heterogeneity analysis, whereas MS-based strategies emphasize molecular depth and network-level insights. These complementary strengths underscore the importance of context-dependent selection or integrative application tailored to specific biological questions and sample characteristics.

Application of single-cell and spatial proteomics has transformed the analysis of the tumor microenvironment (TME) by resolving cellular composition, functional states, and spatial interactions with unprecedented resolution. In breast cancer, imaging mass cytometry enabled construction of the spatial resolved pathology atlas at single-cell resolution by simultaneously detecting dozens of protein markers, revealing that specific cellular neighborhood structures, such as the proximity of immune cells to malignant cells, which were strongly associated with clinical outcomes [154]. In glioblastoma, spatially resolved multi-omics analyses uncovered bidirectional signaling dependencies between tumor cells and host cells, including microglia and neurons, highlighting interaction network inaccessible to bulk approaches [155]. Similarly, integrative single-cell proteo-transcriptomic analyses in refractory small-cell lung cancer revealed malignant neuroendocrine subtypes spatially coupled to immunosuppressive immune niches, providing a rationale for subtype-specific combination therapies [156]. A systematic review summarized the latest strategies of single-cell multi-omics in decoding TME cellular diversity and specifically discussed how observed cellular heterogeneity (e.g., specific stromal cell subpopulations or immunosuppressive microenvironments) can be directly linked to clinical therapeutic resistance mechanisms, providing a theoretical framework for developing TME-targeted combination therapies [157].

Mass spectrometry-based imaging approaches constitute a central pillar of spatial proteomics. Techniques such as mass spectrometry imaging (MSI) enable label-free, untargeted mapping of hundreds of proteins and post-translational modifications directly on tissue sections [158,159]. Expansion-based strategies, including Micro-scaffold Assisted Spatial Proteomics (MASP) [160] and filter-aided expansion proteomics [149,161], have further enhanced protein identification depth and localization accuracy, enabling *in situ* mapping of subcellular and organelle proteomes. These methods have revealed spatially distinct proteomics networks within tumors, such as differences between tumor cores and invasive fronts [159], and enabled analysis of mitochondrial and membrane protein organization [162]. More recently, integration of stable isotope metabolic labeling with spatial proteomics has provided the first spatially resolved measurements of protein turnover rates, offering a dynamic dimension to tissue proteome organization [163].

Spatial multimodal integration represents a major frontier in the field. Combining highly multiplexed protein imaging (e.g., CODEX or MIBI) with sequencing-based spatial transcriptomics allows simultaneous acquisition of functional protein states and underlying transcriptional programs from the same tissue regions [164–166]. Automated platforms such as SM-Omics further streamline tissue processing, imaging, sequencing, and data integration, enabling scalable and reproducible spatial multi-omics analyses and supporting large-scale atlas initiatives [167,168].

Under the overarching goal of constructing comprehensive spatial cellular atlases, the integration of spatial resolution with multi-omics dimensions is enabling a system-level understanding of biological organization. This paradigm has already demonstrated substantial value in both cancer research and

normal tissue biology, accelerating the transition of precision medicine toward a spatially informed era. In oncology, integrated spatial multi-omics analyses have revealed that tumors such as glioblastoma are not homogeneous entities but spatially stratified ecosystems, comprising hypoxic necrotic cores, densely cellular tumor regions, highly infiltrative margins, and distal niches enriched in immune and neural cell populations. Each spatial compartment exhibits distinct molecular programs and cell-cell communication networks, underscoring the functional importance of spatial context [169].

Longitudinal spatial multi-omics studies of acral melanoma have further illustrated how tumor evolution is coupled to spatial remodeling of the immune microenvironment. These analyses traced the geographic expansion of tumor clones from *in situ* lesions to invasive disease while revealing a progressive shift of the immune landscape from a restrained to an exhausted state, thereby identifying critical spatiotemporal windows for therapeutic intervention [170]. In solid tumors such as pancreatic cancer, spatial proteomics and transcriptomic profiling has systematically identified conserved subtypes of cancer-associated fibroblasts (CAFs) with distinct spatial localizations and functions. These CAF subtypes form defined cellular neighborhoods with immune and malignant cells, some fostering immune exclusion and others correlating with favorable clinical outcomes, providing a rational framework for stroma-targeted therapies [171–173].

Beyond cancer, spatial multi-omics has been instrumental in constructing normal tissue atlases. AI and mark study integrating single-cell transcriptomics with multiplexed ion beam imaging generated a spatially resolved multicellular atlas of human bone marrow. This work precisely localized hematopoietic stem and progenitor cell niches and elucidated the spatial organization, molecular characteristics, and combinatorial signaling cues contributed by diverse stromal cell types, including pericytes, osteoblasts, and macrophages, offering a new spatial framework for understanding hematopoietic regulation and blood disorders [174].

Looking forward, the continued expansion and standardization of spatial proteomics technologies, together with advances in data integration algorithms and visualization tools, make the construction of dynamic, high-resolution, multi-omics human cell atlases across development, homeostasis, aging, and disease an increasingly attainable goal. Such atlases will not only deepen our understanding of how cells coordinate within spatially organized tissues but also transform early disease diagnosis, prognostic stratification, and the development of therapies targeting specific spatial microenvironments [167,175–178].

7. Proteomics-driven translational and clinical implications

Proteomics provides a functional layer of information that complements genomics, enabling a more comprehensive and macroscopic characterization of tumors and extending our understanding of cancer biology beyond the scope of genomic analyses. This functional perspective forms a critical foundation for elucidating disease mechanisms and facilitating the development of new therapeutic strategies. Quantitative proteomics captures the activity of oncogenic signaling pathways by measuring the abundance and post-translational modifications of key molecular regulators. For example, increased nuclear factor erythroid 2-related factor 2 (NRF2) phosphorylation reflects activation of NRF2 pathway, while enhanced histone H3 lysine 27 (H3K27) acetylation is indicative of Wnt pathway activation [179,180]. Crucially, the hyperactivation of signaling pathways within malignant cells frequently translates into an increased susceptibility to inhibition by clinically utilized targeted

therapeutics. A prime example is observed in aneuploid cells, a prevalent hallmark of human malignancy, where hyperactivation of the rapidly accelerated fibrosarcoma (RAF)-MAPK/ERK kinase (MEK)- extracellular signal-regulated kinase (ERK) signaling pathway cascade confers a heightened sensitivity to pharmacological agents such as the MEK inhibitor trametinib and the ERK inhibitor ulixertinib. This observation robustly demonstrates that pathway activation directly establishes a critical drug vulnerability [181]. Consequently, the proteomics-driven delineation of these critical signaling dependencies is essential for identifying actionable therapeutic targets, thereby informing and advancing the principles of precision oncology and the clinical management of cancer patients. Thus, to assist researchers to select appropriate technologies for cancer research, we provide a structured comparison of prevailing proteomics strategies across acquisition modes, analytical scales, and spatial dimensions (Supplementary Table S2).

For cancers, specific therapeutic targets have not yet been identified, and effective biomarkers for precision therapy remain lacking. In this context, patient stratification based on proteomics is critical for overcoming these limitations. Integrative multi-omics analyses, encompassing genomics, transcriptomics, epigenomics, and proteomics, classified esophageal squamous cell carcinoma into four distinct subtypes, thereby advancing clinical understanding of this highly aggressive malignancy and providing a valuable resource for future personalized management of esophageal cancer patients [182]. Similarly, the application of proteomics data to improve clinical stratification in gastric cancer has enabled detailed characterization of two gastric cancer phenotypes, revealing differential sensitivities of subtypes to oncogenic signaling pathways and guiding optimal treatment strategies [183]. Moreover, proteomics can be applied in clinical trials to monitor dynamic therapeutic responses more effectively. Changes at the protein level often are highly dynamic than genomic or transcriptomic alterations, and real-time assessment of protein functional states provides an accurate reflection of signaling pathway modulation, facilitating timely adjustment of treatment regimens. Establishing systematic associations between proteomics features and clinical outcomes requires a deep understanding of cancer biology and insight into its therapeutic vulnerabilities, ultimately enabling the discovery of novel treatment avenues with high translational potential and the implementation of individualized therapies.

Drug repurposing aims to identify new therapeutic indications for approved or previously developed drugs. Proteomics offers a more precise approach for identifying protein targets that drive tumor initiation and progression, and is increasingly emerging as a powerful tool for clinical drug repurposing. By leveraging protein–protein interaction networks, proteomics characterizes the topological properties of drug targets, enabling systematic target prediction [184], however, the approach is associated with relatively high false-positive rates, and novel high-throughput databases remain to be fully developed [185]. Moreover, proteomics provides opportunities for cross-cancer drug applications. For instance, while most predicted antigenic epitopes are typically specific to individual patients, integrated pan-cancer analyses have identified five KRAS mutant peptides that generate novel epitopes across four different cancer types, highlighting their potential as shared neoantigens for therapeutic intervention [186]. By applying proteomics technologies, existing drugs can be re-evaluated clinically to uncover previously unreported indications, thereby substantially reducing the time and cost required for drug development and approval, and offering timely and effective treatment options to a broader population of cancer patients. Drug repurposing strategies not only provide novel perspectives for cancer therapy and accelerate the

development of treatment regimens, but also deliver new hope to patients, representing significant economic and societal value.

8. Outlook and artificial intelligence–driven proteomics in precision oncology

Artificial intelligence, as a field of computer science, enables machines to emulate human intelligence and has exerted a profound impact on the transformation of healthcare and other industries [187]. In recent years, the rapid advancement of multi-omics, digital pathology and artificial intelligence has spurred considerable interest in the use of deep learning–based approaches for clinical decision support (Figure 3). While traditional statistical methods are often more intuitive and offer greater transparency for clinical decision-making, unsupervised feature generation strategies based on deep learning can rapidly extract critical information from complex data, such as medical imaging and pathology, facilitating problem-solving across diverse domains and promoting the transition from qualitative to quantitative pathology [188]. Nevertheless, systematic inference of protein networks remains a major challenge due to the large and complex nature of proteomes across most species. However, the continuous development of biological models and computational tools has made such analyses increasingly accessible and reliable [189].

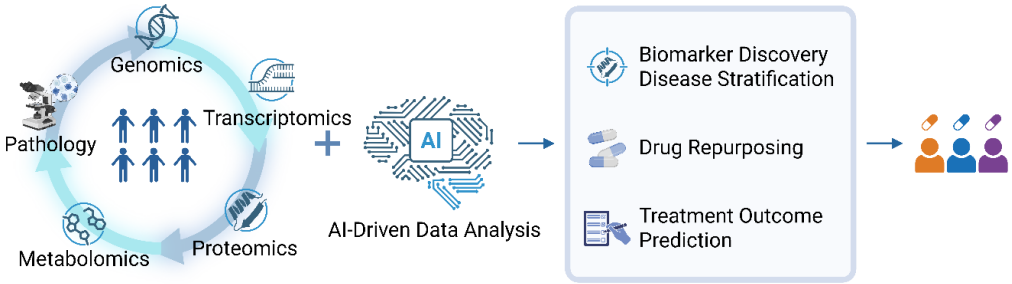

Figure 3. Data-driven and AI-assisted cancer medicine.

In the context of highly heterogeneous advanced solid tumors, machine learning has been applied to distinguish diagnostically relevant morphologies from complex tissue specimens shaped by multiple molecular gradients [190]. Similarly, in the case of the intricate malignant transformation of prostate cancer, machine learning-based predictive models of biomarkers have been constructed to assist clinical decision-making [191]. Furthermore, a pan-cancer cell line proteomics landscape constructed using a deep neural network-based computational pipeline has enabled the identification of cancer vulnerability-associated biomarkers that cannot be captured by genomics or transcriptomics alone, thereby guiding the selection of effective therapeutic strategies [192]. The integration of artificial intelligence is driving proteomics from traditional rule-based and statistical modeling paradigms toward data-driven, representation-learning computational frameworks. Early mass spectrometry analysis relied heavily on handcrafted scoring functions and linear models, which were limited in capturing complex nonlinear spectral features. In contrast, deep learning architectures—such as convolutional neural networks (CNNs), Transformers, and graph neural networks (GNNs)—enable end-to-end learning of high-dimensional representations, resulting in systematic advances in spectrum prediction, sequence inference, and structural modeling [193,194]. For example, Prosit refines database search scoring by learning fragment ion intensity distributions, DeepNovo enhances the accuracy and applicability of de novo sequencing, and DIA-NN

improves signal discrimination and quantitative robustness in complex DIA datasets [195,196]. At the structural and functional levels, AlphaFold leverages attention mechanisms to achieve near-experimental accuracy in protein structure prediction, while DeepGO applies graph neural networks to model protein-protein relationships for network-based functional annotation [197,198]. Collectively, deep learning models have evolved from specialized spectrum interpretation tools into integrated analytical frameworks spanning protein identification, quantification, and functional inference, thereby redefining the computational paradigm of proteomics and enabling deeper mechanistic insight. Looking forward, with the ongoing accumulation of biological datasets and continual advancements in information technology, deep learning is poised to play an increasingly pivotal role in clinical decision support.

Integrative analysis of pathology-transcriptomics-proteomics framework that leverages deep learning applied to H&E images across multiple cancer types has been used to identify predictive histologic features, uncover their molecular drivers, and achieve accurate and generalizable prediction of key clinical outcomes [199]. Consistent with this progress, the development of proteomics-based models for predicting therapeutic outcomes has emerged as a key direction in precision medicine. For example, a phenotypic atlas of tissue morphology in small-cell lung cancer was constructed using a hybrid clustering strategy combined with end-to-end self-supervised deep learning, enabling robust patient subtype classification, risk stratification, and prognostic assessment [200]. Similarly, machine learning models applied to mass spectrometry-based serum proteomics have demonstrated strong potential for predicting immunotherapy efficacy and guiding patient stratification [201]. H&E to protein expression (HEX), an AI model that predicts spatial protein expression from routine H&E histopathology slides, overcome cost and scalability limitations of spatial proteomics. Trained on large paired image-proteomics datasets, HEX accurately infers immune and functional protein markers and significantly improves prognostic and immunotherapy response prediction in non-small cell lung cancer [202]. This approach enables scalable, interpretable spatial biomarker discovery for precision oncology. The integration of proteomics with artificial intelligence allows for efficient and accurate processing of large-scale proteomics datasets, playing a critical role in tumor detection and classification, biomarker discovery, and survival prediction, and thereby strongly advancing the development of personalized medicine [203]. Increasingly powerful artificial intelligence approaches have been widely applied to multi-omics data analysis. Machine learning-riven drug ranking frameworks that integrate proteomics and phosphoproteomics data enable the systematic prediction of anticancer drug efficacy [204]. AI facilitates systematic fusion of proteomics with genomics, transcriptomics, and metabolomics through multimodal learning, latent factor modeling, and graph-based integration strategies. Tools such as MOFA identify latent drivers across omics layers, whereas DIABLO applies multivariate projection methods to model cross-omics feature associations [205,206]. Emerging graph neural networks and variational autoencoder-based frameworks further reconstruct cross-layer regulatory networks within shared embedding spaces [207–209]. These integrative strategies enhance systems-level interpretability and enable more comprehensive molecular stratification in disease research and precision medicine. AI-driven multi-omics integration is thus transitioning from correlation-based analyses toward mechanism-oriented modeling frameworks.

Looking ahead, the convergence of proteomics and artificial intelligence is poised to fundamentally transform precision oncology. AI-driven methods, particularly deep learning, offer powerful capabilities for extracting biological meaning from increasingly large, complex, and high-dimensional proteomics

datasets, including single-cell, spatial, and multi-omics profiles. These approaches enable automated pattern recognition, biomarker discovery, pathway inference, and therapeutic response prediction that are difficult to achieve with conventional analytical frameworks. Integration of proteomics with AI-powered digital pathology and imaging further allows the linking of molecular states to tissue architecture and clinical phenotypes, facilitating scalable and cost-effective translation into clinical practice. As standardized datasets, robust computational models, and interpretable AI frameworks continue to mature, proteomics-informed AI systems are expected to play a central role in clinical decision support, dynamic patient stratification, and the development of truly personalized, mechanism-driven cancer therapies.

Supplementary data

Supplementary tables summarizing cancer biomarkers from MS-based proteogenomic analyses (Table S1) and a comparative overview of proteomics methodologies (Table S2) are provided with this article.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization, Bingbing Hao; literature collection, Bingbing Hao, Yixuan Shi, Songting Yang and Yale Chen; writing—original draft preparation, Bingbing Hao, Yixuan Shi, Songting Yang and Yale Chen; writing—review and editing, Bingbing Hao and Yixuan Shi; visualization, Yixuan Shi and Songting Yang; supervision, Bingbing Hao; funding acquisition, Bingbing Hao. Jiyun Chen contributed to manuscript revision. Yixuan Shi, Songting Yang and Yale Chen contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no competing interests.

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