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Application and prospects of proteomic technology in inflammation: a review

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ABSTRACT

Proteomics is a new technology that has been widely applied in the field of life and health science. It effectively addresses issues related to the impact of dietary structure on organs, tissues, and cells, as well as the changes in proteins in various organs, tissues, and cells under disease conditions. The differential proteins identified through proteomics can serve as disease biomarkers and target proteins affecting health and can be used for disease diagnosis and health regulation. In this paper, the application of proteomics in the field of inflammation in recent years was summarized, especially in the therapeutic target and mechanism of action, which opens up a new way for more effective prevention, diagnosis, and treatment of inflammation, and provides medical protection for human life and health.

1. Introduction

Proteomics is a science that studies the composition and changes of proteins in cells, tissues, or organisms based on the proteome[1-2]. The study of proteomics mainly includes two aspects: quantitative research and qualitative research. Qualitative research focuses on the composition, structure, function, post-translational processing, modification, distribution, localization, and interactions of proteins. Quantitative research is primarily concerned with accurate and reliable quantitative analysis of proteins[3-4]. With the development of high-throughput proteomics technology, it has been widely utilized in the fields of biology, medicine, pharmacy, nutrition science, agronomy, botany, microbiology, and food science, gradually becoming a significant driving force for scientific advancement.

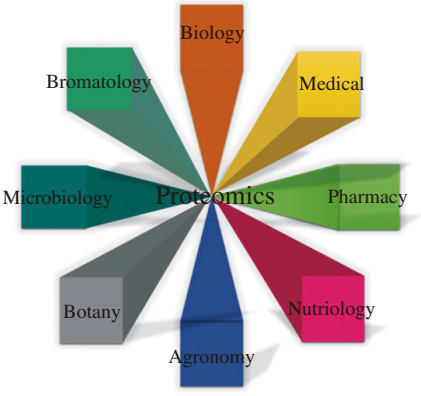

Fig. 1 Application of proteomics.

The proteomics methods include labeled and label-free quantification. Labeled quantification is to label the peptide by isotope labeling reagent, using mass spectrometry for qualitative and quantitative analysis, and combining bioinformatics technology to find that different proteins contain biological information[5-6]. The relevant workflow of labeled quantitative proteomics is shown in

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Fig. 2. The commonly used labeling quantitative methods include stable isotope labeling by amino acids in cell culture (SILAC), isobaric tags for relative and absolute quantification (iTRAQ), and tandem mass tags (TMT). At present, TMT-labeled quantification can simultaneously quantify 16 samples and more than 10 000 proteins. If there are too many samples, label-free quantification is required. Label-free quantitative samples do not need labeling, sample demand is the small, low cost of consumables, suitable for the detection of more samples, it has been widely used in protein quantitative research. Based mass spectrometry (MS) of proteomics technology has thoroughly changed the way of protein analysis and can simultaneously detect thousands of proteins in a variety of samples, such as tissues, cells, or biological fluids, extending its interface role to a wide and diverse field of scientific and technological research[7].

Depending on the subject of study, proteomics is divided into three types: expression proteomics, structural proteomics, and functional proteomics[8]. Expression proteomics studies changes in protein expression between different tissues or cells. For example, using expression proteomics technology to reveal the expression profile of proteins in biological or clinical samples, to discover key proteins and molecular mechanisms related to diseases[9]. Structural proteomics elucidates structure-function relationships of uncharacterized gene products based on three-dimensional protein structures. It proposes biochemical and cellular functions of unannotated proteins to identify potential targets for drug design and protein engineering[10]. Commonly used methods include nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography. Functional proteomics studies the interaction, localization, and modification of proteins. For example, modified proteomics refers to the identification of different types of modifications on proteins after the completion of protein synthesis, including glycosylation modification, acetylation modification, phosphorylation modification, etc., to reveal the dynamic changes of proteins in signal transmission[11-12].

Inflammation is a complex defense response of the body to external stimuli, which is associated with most diseases[13]. Excessive inflammation can lead to complications such as atherosclerosis, rheumatoid arthritis, diabetes, and tumors[14-16]. The mechanism of inflammation is complex and dynamic, making it challenging to elucidate through traditional molecular biology methods. It is of great significance to reveal the mechanism and target of inflammation through omics technology for inflammation and inflammatory diseases. This review summarized the application of proteomics technology on the study of inflammation in the last 3 years, which opens up a new path for revealing the complex molecular regulatory network, screening biomarkers and therapeutic targets of inflammation.

2. Application of proteomic techniques in inflammation

2.1 The discovery of biomarkers

During different stages of inflammation, the expression of proteins in the body changes rapidly in response to extracellular nutritional changes and various stimuli. Macrophages are vital immune cells in the body's immune system, with a strong phagocytosis ability, and play a key role in the early stage of inflammation to resist foreign invaders[17-18]. The detection of cell proteome in macrophages is of great significance for the prevention and diagnosis of early inflammation. Through the analysis of cell proteome, researchers can identify differentially expressed proteins and pathways that are involved in inflammatory responses. These proteins and pathways may serve as potential biomarkers for diagnosing and monitoring inflammatory diseases, as well as targets for developing new treatments. Mulvey et al.[19] used proteomics to find that interleukin (IL)-1β was the only protein found to be significantly up-regulated after lipopolysaccharides (LPS) stimulation of THP-1 cells for 2 h, and its abundance remained elevated for 24 h. Therefore, IL-1β could be used as a biomarker for the early diagnosis of inflammation. After 4 h of LPS stimulation, three proteins were also up-regulated. After 6 h of LPS stimulation, 32 proteins were up-regulated, including 17 known interferon (IFN)-inducible proteins. Poly(ADP-ribose) polymerase (PARP) 14 and PARP9 were also significantly up-regulated at this stage. After 12 and 24 h of LPS stimulation, in addition to the differential proteins described above, interferon-stimulated gene (ISG) 20, guanylate binding protein (GBP) 3, epithelial stromal interaction 1 (EPSTL1), matrix metalloproteinase (MMP) 9, centrin 3 (CETN3), and more differential proteins were changed (Table 1). Iwata et al.[20] performed proteomics studies on RAW264.7 and THP-1 cells treated

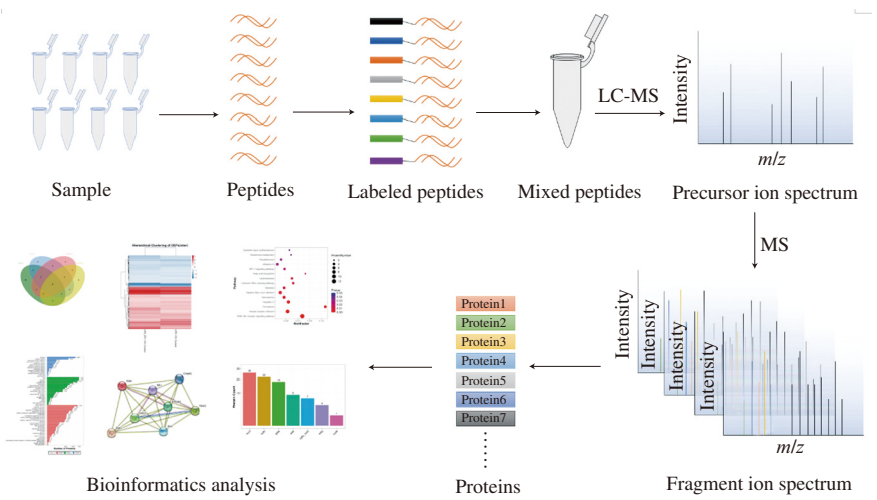

Fig. 2 Workflow chart of labeled quantitative proteomics.

with IFN-γ and IL-4, analyzing changes in the proteome at 0, 12, and 24 h. The results showed that PARP9 and PARP14 were closely related to inflammation, which further suggested that PARP family members may be key factors in early inflammation, and whether the PARP family can be used as a biomarker for early inflammation.

Phosphorylated proteins play an important role in signal transduction among the complex regulatory mechanisms in the body, which provides new insights into the complex regulatory mechanisms of diseases[21-22]. The expression of phosphorylated proteins in cells is detected to predict the pathways involved in intracellular signal regulation and the key target proteins. Song et al.[23] used TiO_2 beads to collect phosphorylated peptides and performed mass spectrometry detection. The results showed that phosphorylated proteins treated with LPS for 45 min and LPS for 24 h were significantly different. Welz et al.[24] analyzed the entire proteome and phosphorylated peptides of TNF-induced human monocytes and found that 148 proteins and 569 phosphopeptides were significantly regulated. Luo et al.[25] analyzed the whole proteome and phosphorylated peptides of RAW264.7 cells induced by LPS to detect 219 differential proteins and 405 differential phosphorylated proteins. These proteins included major regulators of inflammatory signal transduction proteins such as inhibitor of kappa B kinase (IKK), nuclear factor kappa-B (NF-κB), interleukin receptor associated kinase (IRAK), Inhibitor of NF-κB (IKB), phosphoinositide 3-kinase (PI3K), protein kinase B (AKT) etc. Both the whole proteome and the phosphorylation proteome can be effectively applied to study protein phosphorylation patterns in monocytes, and these results provide new candidates and evidence for the complex molecular modulation mechanism of inflammation.

In addition, different stimuli lead to different polarized types of macrophages, and protein expression within these different polarized types of macrophages is also different[26-27]. The study found that M1 macrophages are particularly important, they are closely related to chronic tissue inflammation, including atherosclerosis, obesity, metabolic syndrome, asthma, allergies, and autoimmune diseases. The balance between M1 and M2 macrophages is considered critical for controlling the progression and clinical outcome of macrophage-mediated inflammatory diseases[28-29]. Huang et al.[28] used proteomics technology to find that M1 macrophages caused much pro-inflammatory protein expression increased, including interferon-induced protein with tetratricopeptide repeats (IFIT) 1, IFIT2, IFIT3 and the products of 31 genes under the transcriptional controlled by interferon regulatory factor (IRF) 1. Li et al.[30] analyzed polarized cells by label-free quantitative proteomics technology and found that intracellular protein expression showed obvious changes in different polarized cells. The expressions of UMP-CMP kinase 2 (CMPK2), radical *S*-adenosyl-*L*-methionine domain 2 (RSAD2), retinoic acid-inducible gene-1 (RIG-1), and DExH-Box helicase 58 (DHX58) were highly expressed in M1 and M2 THP-1 cells. The proteins IFIT1, IFIT2, IFIT3, cluster of differentiation (CD) 14, CD38, CD40, and C-X-C motif chemokine ligand (CXCL) 10, which have been reported as M1 biomarkers[31-32]. Transglutaminase type 2 (TGM2), the only protein upregulated in M2 THP-1 cells, was also used as an M2 biomarker. However, nitric oxide synthase (NOS) 2, CD40, and CD86 have been reported as markers of M1 macrophages, which are uniquely upregulated in M1 RAW264.7 cells[33]. Other proteins prostaglandin-endoperoxide synthase (PTGS) 2, plasminogen activator surface receptor (PLAUR), signal transducer and activator of transcription (STAT) 5, GBP4, erythropoietin producing hapatocellular receptor A2 (EPHA2), caspase-6 (CASP6) and CMPK2 may also be involved in the M1 polar process. Table 1 summarizes the potential biomarkers of inflammation mined by proteomics technology in the last 3 years.

Novel biomarkers can be used not only as indicators for disease diagnosis and later judgment but also as targets for treatment. For example, when macrophages are stimulated, the expression of CMPK2 in mitochondria increases, leading to increased levels of the deoxycytidine triphosphate involved in mitochondrial DNA synthesis. The newly generated DNA is oxidized by reactive oxygen species (ROS), which then activates the NOD-, LRR- and Pyrin Domain-Containing Protein (NLRP) 3 to produce inflammation[34]. As biomarkers, these proteins can help scientists identify and track biological processes or disease states to better understand and treat diseases. As drug targets, these proteins can be used to design and develop new drugs to treat specific diseases or pathological processes. The dual role of these proteins provides new insights and methods for inflammation research, which is expected to lead to breakthroughs in the prevention and treatment of inflammation-related diseases.

2.2 The discovery of therapeutic targets

Therapeutic targets for the treatment of inflammatory diseases are currently receiving significant attention. Proteins are expressed differently in different cell lines or tissues, resulting in different protein changes under the same stimulus. Different stimuli also lead to different protein expression[41]. This presents a significant challenge in the identification of therapeutic targets for inflammation. Some drugs can simultaneously on multiple biological molecules or signaling pathways, resulting in a variety of biological effects[42-43]. This multi-target action can enhance the efficacy of drugs, but also increase the side effects of drugs, which led to poses a huge problem for the treatment of inflammation. However, proteomic technology can effectively address this issue. Through the screening of a key protein of proteomics results and to validate the use of biological molecular biology methods, which can effectively determine the inflammation of potential therapeutic targets.

Li et al.[44] used proteomics technology to study polycystic ovary syndrome and found that S100 calcium binding protein A9 (S100A9) was highly expressed in the polycystic ovary syndrome group, and overexpression of S100A9 could promote NF-κB signaling pathway, indicating that S100 is an effective target to inhibit inflammation. Liao et al.[45] used proteomics techniques to find that near-infrared radiation enhances the expression of citrate synthase (CS) in mitochondrial respiratory proteins. Inhibition of citrate synthase can reduce the inhibition of macrophage polarization to M2, thus indicating whether CS can be used as a target protein for an inhibitory macrophage program. It also reveals an insight into the discovery of new functions for proteins. Zhang et al.[46] found that galectin-1 is a target of shikonin by proteomics technology. Down-regulation of galectin-1 expression can increase the phosphorylation level of c-Jun N-terminal kinase (JNK), suggesting that galectin-1 may have a negative regulatory effect on JNK activation. This also reveals that galectin-1 can also act as a negative regulatory target of inflammation. Ortiz et al.[47] used proteomics to find that NF-κB-inducing kinase (NIK)

Table 1
Proteomics methods were used to detect potential biomarkers of inflammation.

Cell types	Stimulants	Time (h)	The proteomics approach	Potential biomarkers	Reference
THP-1	LPS	2	TMT, LC-MS/MS	IL-1β	[19]
	LPS	4		IL-1β, IFIT2, IFIT3, CXCL10	
	LPS	6		IL-1β, IFIT2, IFIT3, IFIH1, CXCL10, SP100, CMPK2, RSAD2, MX1, Sequestosome 1, EPSTI1, MT2A, PARP9, PARP14, PDCD4, KDM4A, CLEC11A	
	LPS	12		IL-1β, IFIT1, IFIT2, IFIT3, IFIH1, IFI16, CXCL10, CMPK2, ISG20, GBP3, EPSTL1, MMP9, MX1, PDCD4, CLEC11A, IRF8, RET, VLDLR, PTPRF, CETN3	
	LPS	24		IL-1β, IFIT2, IFIT3, IFIT5, CMPK2, ISG15, EPSTL1, MMP9, MX2, SRC, GBP2, GBP3, PDCD4, CLEC11A, RET, TMOD1, PTPRF, TPX2, MEF2D, GTSF1, CENPF, GFI1, CD37, ST14, CD37, Cyclin-B2, NUSAP1, ST14	
Monocytes	TNF	48	LC-MS/MS	IDO1, SIG10, MYH11, SRSF2, Ladinin-1, CD82, CLIC4, KYNU, AIM1	[24]
			TiO_2, LC-MS/MS	GSK3	
RAW264.7	LPS	4	LFQ, LC-MS/MS	PFKL, PGK1, GYS1, ACC, HSL, LDHA, RAB14, PRKAA1, IKKs, NF-κB, IRAK, IKB, PI3K, AKT, MCL-1, BID, Sequestosome 1	[25]
THP-1	IFN-γ/LPS	–	LFQ, LC-MS/MS	IRF1, IFIT1, IFIT2, IFIT3	[28]
THP-1	IFN-γ, LPS	48	LFQ, LC-MS/MS	CMPK2, RSAD2, CD14, CXCL10, USP18, CD274, RSAD2, IDO1, GBP1, TAP1	[30]
THP-1	IL-4, IL-13	72	TiO_2, LC-MS/MS	CMPK2, RSAD2, TGM2, Glypican 4, LPL, SCAM1, Drebrin 1	
THP-1	PMA	16	LC-MS/MS	CD36, CD11b, MAPK1, CDK1, PRKACB	[35]
		48		TBK1, IRF3, IL-1β, SCRB1, ISG15, LYN, COPS5, MRPL3, GTPase KRas	
		72		GOT1, PSAT1, AARS, CBS, IMPDH1	
THP-1	LPS	24	TMT, LC-MS/MS	APMAP	[36]
RAW264.7	LPS	28	iTRAQ, LC-MS/MS	PRMT	[37]
THP-1	IFN-α	48	LFQ, LC-MS/MS	IFIT1, IFI22, IFI44L, IFIT3, IFI16, MX1/2, OAS2/3, ISG15	[38]
THP-1	IL-33	4	TMT, TiO_2, LC-MS/MS	NOC2L (S49, S56), NCOA2 (S736), NUCKS1 (S19), NCOR2 (S149, S152), TP53BP1 (S366), MTDH (S308), YAP1 (T110), EIF4G1 (S1147), BCLF1 (S531), ACL6A (S233)	[39]
THP-1	IL-4	24	LFQ, LC-MS/MS	TGM2, ALDH1A2, FABP4, CREBBP, CRABP2	[40]
	LPS and IgG-OVA			SPHK1, CXCL1, SCRB1, MMP9, THBS1, Cathepsin D, Plasminogen, CCR1	
	IL-10			MSR1, Dysferlin, PYCR1, CXCL8, NCF2, GGA2, Presenilin-1	
	NECA and LPS			VEGFA, MMP1, GDF15, ATF3, PLAU, MGMT	

Note: AARS, aminoacyl-tRNA synthetase; ACC, acetyl-CoA carboxylase; ACL6A, actin-like protein 6A; ALDH, aldehyde dehydrogenase family; APMAP, adipocyte plasma membrane associated protein; ATF3, activating transcription factor 3; BCLF1, Bcl-2-associated transcription factor 1; CBS, cystathionine *β*-synthase; CDK1, cyclin-dependent kinase 1; CENPF, centromere protein F; CLEC, C-type lectin domain family; CLIC4, chloride intracellular channel 4; COPS5, constitutive photomorphogenic-9 signalosome; CRABP2, cellular retinoic acid-binding protein 2; CREBBP, CREB binding protein; EIF4G1, eukaryotic translation initiation factor 4 gamma 1; GDF15, growth differentiation factor 15; GFI1, growth factor independent 1; GOT1, glutamate oxaloacetate transaminase 1; GTSF1, gametocyte specific factor 1; GYS1, glycogen synthase 1; HSL, hormone-sensitive lipase; IDO1, indoleamine 2,3-dioxygenase 1; IMPDH1, inosine monophosphate dehydrogenase 1; KDM4A, lysine specific demethylase 4A; KYNU, kynureninase; LDHA, lactate dehydrogenase A; LYN, tyrosine-protein kinase Lyn; MCL-1, myeloid Cell Leukemia-1; MEF2D, myocyte enhancer factor 2D; MGMT, O^6-methylguanine-DNA methyl-transferase; MRPL3, mitochondrial ribosomal protein L3; MT2A, metallothionein 2A; MTDH, metadherin; MX, myxovirus resistant; MYH11, myosin-11; NCF2, neutrophil cytosolic factor 2; NCOA2, nuclear receptor coactivator 2; NCOR2, nuclear receptor co-repressor 2; NOC2L, nucleolar complex associated 2 homolog; NUCKS1, nuclear casein and cyclin-dependent kinase substrate 1; NUSAP1, nucleolar and spindle associated protein 1; OAS, 2′-5′oligoadenylate synthetase; PDCD4, programmed cell death protein 4; PFKL, phosphofructokinase liver type; PGK1, phosphoglycerate kinase 1; PLAU, urokinase-plasminogen activator; PMA, phorbol-12-myristate-13-acetate; PRKACB, protein kinase A catalytic subunit beta; PRMT, protein arginine methyltransferase; PTPRF, protein tyrosine phosphatase receptor type F; PYCR1, pyrroline-5-carboxylate reductase 1; RET, proto-oncogene tyrosine kinase receptor; SCAM1, secretory carrier-associated membrane protein 1; SCRB1, scavenger receptor class B member 1; SPHK1, sphingosine kinase 1; SRC, steroid receptor coactivator; SRSF2, serine/arginine-rich splicing factor 2; ST14, suppressor of tumorigenicity 14; TAP1, transporters associated with antigen processing 1; THBS1, thrombospondin 1; TMOD1, tropomodulin 1; TP53BP1, tumor protein p53 binding protein 1; TPX2, targeting protein for xenopus kinesin-like protein 2; USP18, ubiquitin specific peptidase 18; VEGFA, vascular endothelial growth aactor A; VLDLR, very low-density lipoprotein receptor; YAP1, yes-associated protein 1.

promotes kidney injury by promoting inflammation and cell death, suggesting that NIK is a promising new therapeutic target.

The potential candidate targets were summarized (Table 2) and the results showed the heat shock protein (HSP) family (HSP60, HSP90), guanylate binding protein (GBP) family (GBP1, GBP2, GBP4), interferon-activated gene (IFI) protein family (IFIH1, IFI202, IFI204), caspase protein family (CASP6, CASP8), chemokine protein family (CCL3, CCL4, CCL9), chemokine (C–X–C motif) ligand protein family (CXCL1, CXCL2, CXCL8), matrix metalloproteinase protein family (MMP1, MMP9) and S100A protein family (S100A8, S100A9) are involved in the regulation of inflammatory response. nucleotide-binding oligomerization domain (NOD) 1, NOD2, and NLRP3 in NOD receptor signaling pathways were also detected by different cell lines. In addition, there are some special proteins, such as galectin-1, kruppel-like factor 4 (KLF4), second mitochondria-derived activator of caspases (SMAC), beta 2-microglobulin (B2MG), etc., which have been detected by proteomic techniques for inflammation regulation. TNF-receptor-associated factor (TRAF) 1, chemokine (C-C motif) receptor type (CCR) 1, macrophage scavenger receptor 1 (MSR1), and other proteins have been reported in many literatures. All of these proteins were found by proteomics technology, and all of them have different degrees of correlation with inflammation. Therefore, whether these proteins can be used as therapeutic targets for inflammation in the clinic is worthy of further research.

2.3 The discovery of drug targets and mechanisms

Proteomics technology has been applied to the study of inflammatory signaling pathways, which can determine the location

Table 2
Proteomics methods were used to detect potential therapeutic targets of inflammation.

Cell types	Stimulants	The proteomics approach	Potential targets	Reference
THP-1	Near-infrared	LC-MS/MS	CS	[45]
THP-1	*Rickettsia parkeri*, *Rickettsia africae*, *Rickettsia massiliae*	LFQ, LC-MS/MS	GBP1, GBP2, GBP4, OAS2, OAS3, OASL, MDA5, DHX58, TRIM25, ISG15	[48]
THP-1	*Legionella pneumophila*	SILAC, LC-MS/MS	MX1, Galectin-8, RIG-1, TP53	[49]
THP-1	*Candida albicans*	SILAC, LC-MS/MS	MAP2K2, SYK, STK3, MAP3K2, NDKA, SRPK1	[50]
THP-1	EBOV-*Makona*	SILAC, LC-MS/MS	SP1, KLF4, HIF1A	[51]
	RESTV		SP1, KLF4	
RAW264.7	*Burkholderia pseudomallei*	LC-MS/MS	CXCL2, TNFR2, CCR1, G-CSF, TRAF1, complement C3, GPS1, IRAK1, AP3B2, CASP6, CARD9	[52]
RAW264.7	Silica	TMT, LC-MS/MS	SPP1, HMGB3, hnRNP AB	[53]
RAW264.7	MetQ	SILAC, LC-MS/MS	SRC, CCL9, PPIP1, Neurabin-2	[54]
RAW264.7	Wild-type/Tat-mutant *Brucella*	LFQ, LC-MS/MS	IFIH1, IFI202, IFI204, ISG15, PTGS2, TRAF1	[55]
RAW264.7	LPS	TMT, Lip-MS	HSP60	[56]
RAW264.7	SiO_2	iTRAQ, LC-MS/MS	CASP8, HSP90, CCL3, CXCL2, CCL4, NOD2	[57]
RAW264.7	Graphene oxide	SILAC, LC-MS/MS	LPL, Lysozyme 1	[58]
RAW264.7	Docosahexaenoic acid	LFQ, LC-MS/MS	GPR120, RAS, MEK	[59]
RAW264.7	*Listeria monocytogenes*	LC-MS/MS	MRPS35, RPL22L1	[60]
RAW264.7	*B. pseudomallei*	TMT, LC-MS/MS	PGM1, PKM, PGK1	[61]
RAW264.7	*Mycobacterium tuberculosis* Rv1987	LC-MS/MS	Rv1987	[62]
RAW264.7	*trans*,*trans*-2,4-decadienal	LFQ, LC-MS/MS	HSP90, 14-3-3ζ	[63]
Dusp1-knockdRAW264.7	LPS	TiO_2, LC-MS/MS	Protein tyrosine phosphotase 1B, mitogen-activated protein kinase 1	[64]
Macrophages	LPS	SEC, LC-MS/MS	PARP9	[65]
Macrophage	IL-4	LC-MS/MS	MSR1	[66]
A549	SMAC knocked	LC-HR-MS/MS	SMAC	[67]
MM6	miR-328 knocked	TMT, LC-MS/MS	HMGB1, S100A9, NOX2, TLR2	[68]
SW620	Shikonin	iTRAQ, LC-MS/MS	Galectin-1	[46]
ReN	TNF-α or IL-1β	LC-MS/MS	PSMB8, B2MG	[69]
HRECs	Anti-PlGF antibody	TMT, LC-MS/MS	PRDX6, HMOX1, NQO1, YES1	[70]
Caco-2	Aflatoxin M1, ochratoxin A	iTRAQ, LC-MS/MS	APOD, HCCS, SLC11A2	[71]
MEPiC and MCF10A	IL-1β, TNF-α, and IL-6	2D-DIGE, Nano LC-ESI-MS/MS	ILEU, S100A8, S100A9, SOD2	[72]
Hs578T	Overexpression of NOD1 or NOD2	LFQ, LC-MS/MS	NOD1, NOD2	[73]
BMECs	LPS	iTRAQ, LC-MS/MS	NLRP3	[74]
LoVo	Shikonin	Quantitative	NEMO/IKKβ	[75]
HBEpC	O_3	Nano LC-QTOF-MS/MS	AK1BA	[76]
U937	Fusobacterium nucleatum AI-2	TMT, iTRAQ, LC-MS/MS	TNFSF9	[77]

Note: AK1BA, aldo-keto reductase family 1 member B10; AP3B2, adaptor related protein complex 3 beta 2; APOD, apolipoprotein D; CARD9, caspase aecruitment domain family member 9; G-CSF, granulocyte colony stimulating factor; GPR120, G-protein coupled receptor 120; GPS1, COP9 signalosome complex subunit 1; HCCS, holocytochrome c synthase; HMGB, high mobility group box; HMOX1, heme oxygenase 1; hnRNP AB, heterogeneousnuclear ribonucleoprotein AB; ILEU, leukocyte elastase inhibitor; LPL, lipoprotein lipase; MAP2K2, mitogen activated protein kinase kinase 2; MEK, mitogen-activated extracellular signal-regulated kinase; MRPS35, mitochondrial ribosomal protein S35; NDKA, nucleoside diphosphate kinase A; NOX2, NADPH oxidases 2; NQO1, NAD(P)H: quinone oxidoreductase 1; PGM1, phosphoglucomutase 1; PKM, pyruvate kinase M; PPIP1, proline-serine-threonine phosphatase-interacting protein 1; PRDX, peroxiredoxin; PSMB8, proteasome subunit beta 8; RAS, rat sarcoma; RPL22L1, ribosomal protein L22 like 1; SLC11A2, solute carrier family 11 member 2; SPP1, secreted phosphoprotein 1; SRPK1, serine/arginine protein-specific kinases 1; SYK, spleen tyrosine kinase; TNFSF9, TNF superfamily member 9; TP53, tumor antigen p53; TRIM25, tripartite motif containing 25; YES1, YES proto-oncogene 1.

of therapeutic targets in the inflammatory signaling pathway to better understand the molecular mechanism of inflammation. By analyzing changes in protein expression, post-translational modification, and protein-protein interactions in cells or tissues under different inflammatory conditions, as well as the roles of key proteins in signaling pathways, special biologics and drugs can be targeted to exert anti-inflammatory effects by inhibiting relevant signaling pathways.

2.3.1 NF-κB/MAPK signaling pathway

Toll-like Receptors (TLRs) act as membrane-recognition receptors to recognize pathogen-related molecular patterns[78]. It binds to intermediate adaptor proteins and rapidly activates intracellular signaling cascades, eventually leading to the production of inflammatory cytokines and chemokines[79]. As an important transcription factor of the immune activation signaling pathway, the NF-κB family can be activated by myeloid differentiation factor (MyD88)-dependent and non-MyD88-dependent signals, and the signaling components and biological functions of the two pathways are different[80-82]. The relevant mechanism is shown in Fig. 1. However, signaling pathways are composed of many components, and studying signaling pathways solely through traditional techniques is often insufficient. Proteomics technology can address this issue by identifying the signaling pathways and molecular mechanisms involved. Welz et al.[24] proved that glycogen synthase kinase 3 (GSK3) could target the NF-κB signaling pathway. Zhang et al.[83] performed thermal proteome profiling to locate the target proteins of Artone and

found that Artone directly targeted ASF1a at K4, K9, K18, and K27 to regulate histone H3 PTMS, leading to the inhibition of NF-κB signaling pathway and the inactivation of microglia. This is a unique anti-neuritis mechanism discovered by proteomics. Zhao et al.[84] demonstrated that share tripartite motif-containing protein (TRIM) 32-mediated NF-κB activation was dependent on the deubiquitination enzyme OTULIN through proteomics technology, confirming a novel inflammatory regulatory mechanism.

Mitogen-activated protein kinase (MAPK) signaling pathway is an evolutionally-conserved serine/threonine protein kinase in cells that can be activated in response to various extracellular stimuli and regulate a variety of cellular activities, such as inflammatory response, immune regulation, and cell proliferation[85]. The MAPK family consists of three major kinases: extracellular signal-regulated kinase 1/2 (ERK1/2), JNK, and p38 Mitogen-activated Protein Kinase (p38MAPK). Activator protien-1 (AP-1) is a downstream transcription factor of the MAPK signaling pathway, which regulates inflammation by regulating the expression of related genes[86-88]. The relevant mechanism is shown in Fig. 1. Zhao et al.[89] performed proteomics technology and found that seabuckthorn polysaccharides can reduce LPS-induced inflammation by inhibiting the phosphorylation of the MAPK/NF-κB signaling pathway and related proteins. Ti et al.[90] performed proteomics technology and found that sesquiterpenoids in turmeric exert anti-influenza effects through the NF-κB/MAPK and the RIG-1/STAT1/2 signaling pathways. Wang et al.[91] used proteomics technology and found that carnosic acid could not only inhibit NF-κB/MAPK signaling pathway but also inhibit forkhead box-O (FOXO) 1/3 related proteins, which further confirmed the anti-inflammatory mechanism of carnosic acid and provided a new theoretical basis for the clinical study of carnosic acid.

2.3.2 JAK/STAT and IFN signaling pathway

Janus kinase (JAK)/STAT and INF signaling pathways are two closely related signaling pathways that play important roles in the immune system and inflammation processes. JAK-STAT signaling pathway is a cytokine signaling pathway that has attracted much attention in recent years and plays an important regulatory role in cell proliferation, apoptosis, differentiation, and immune response[92]. IFN is a potent cytokine and a key component of the first line of defense against viral infection, which achieves inflammation and immune control mainly through the direct induction of anti-pathogen molecular countermeasures that can inhibit viral replication[93].

IFN signaling pathways are classified into classical and non-classical types. In the classical IFN signaling pathway, IFN binds to the type 1 interferon receptor (IFNAR) which is composed of IFNAR1 and IFNAR2, to initiate signaling. IFNAR is phosphorylated and subsequently activates the JAK-STAT signaling pathway. Activated JAK can bind to the SH2 domain of STATs and phosphorylate STATs, leading to their trimerization or dimerization, followed by nuclear translocation. These two different transcriptional complexes regulate the expression of different IFN-stimulated genes in a sequence-dependent manner[92]. Phosphorylated STAT1, STAT2, and IRF9 form a heterotrimeric complex, ISGF3, which enters the nucleus and binds to the interferon-stimulated response element (ISRE) motif, activating ISG transcription. The two phosphorylated STAT1 form a homodimeric complex that binds to the gamma interferon-activated sequence (GAS) motif to activate proinflammatory gene expression[94-95]. In non-classical IFN signaling pathways, IFN can also induce the expression of a group of genes independent of STATs, such as MAPKs and PI3K signaling pathways, which indirectly induce inflammation[96]. The relevant mechanism is shown in Fig. 3. Iwata et al.[20] used proteomics and transfection techniques to discover the regulatory relationship between PARP9, PARP14, and IFN pathway-related molecules (JAK1, JAK2, STAT1, and STAT6). Silencing PARP9 can inhibit proinflammatory gene expression and STAT1 phosphorylation in cells, and silencing PARP14 can induce proinflammatory gene and STAT1 phosphorylation in cells, further improving the JAK/STAT signaling pathway. Tao et al.[97] found that the ShuFengJieDu capsule could inhibit the inflammatory response of RAW264.7 cells infected with H1N1 by IFN/JAK-STAT and NF-κB/MAPK signaling pathway through proteomics technology. This study not only clarified the inflammatory mechanism of RAW264.7 cells infected with H1N1 but also confirmed the anti-inflammatory mechanism of the ShuFengJieDu capsule.

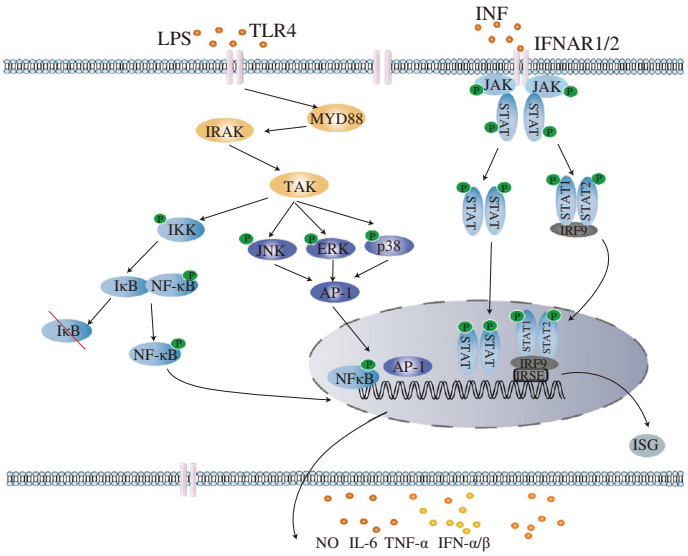

Fig. 3 NF-κB/MAPK/JAK/STAT signaling pathway.

2.3.3 RIG-I like receptors and TNF signaling pathway

The members of RIG-I-like receptors include RIG-I, melanoma differentiation-associated gene 5 (MDA5), laboratory of genetics and physiology 2 (LGP2), which can recognize foreign RNA and activate the downstream interferon signaling pathway[98]. Both RIG-I and MDA5 contain two N-terminal CARD domains, which can facilitate their interaction with other molecules containing the domain. The interaction of these domains promotes RIG-I/MDA5 binding to an important downstream adaptor molecule mitochondrial antiviral signaling (MAVS) protein and activates its downstream signaling molecules[98-99]. MAVS protein is an adaptor molecule that plays a key role in inflammation regulation and antiviral innate immunity. Activated MAVS protein transduce signals to the downstream TRAF3, TANK-binding kinase 1 (TBK1), and IKK complexes, which then phosphorylate IRF3/7 and translocate to the nucleus to induce type I interferon production. Activated MAVS also transduce signals

to IKK complexes by TRAF2 and TRAF6, which ultimately leads to the activation of the NF-κB signaling pathway[100-101]. The relevant mechanism is shown in Fig. 4. Ti et al.[90] found that sesquiterpenes in turmeric exert anti-influenza and anti-inflammatory activities by inhibiting the RIG-I signaling pathway using proteomics technology. Zhou et al.[102] performed proteomics technology and found that Forsythia forsythia could exert anti-inflammatory effects through the RIG-I/NF-κB signaling pathway. Thus, this pathway also plays a very important role in regulating the innate immune response.

The IFN signaling pathway is a signaling pathway mediated by interferons that play an important role in the immune system and inflammation processes[103]. IFNAR can be divided into two subunits, IFNAR1 and IFNAR2. When TNF trimers bind to the extracellular region of tumor necrosis factor receptor 1 (TNFR1), SODD in the intracellular region is released. The intracellular death domain of TNFR1 is combined with the TRADD death domain binding protein to form the TNFR1/TRADD complex. A series of receptor-associated proteins including Fas-associated death domain protein (FADD), target tumor necrosis factor receptor-associated factor 2 (TRAF2), and report or interacting proteins (RIP), are successively recruited to the complex, triggering the activation of downstream signaling pathways, which aggravates the inflammatory cascade. TNFR2 recruits TRAF2 together with TRAF1, cIAP1, and cIAP2 to form a complex that activates downstream signaling pathways such as NF-κB, MAPK, and AKT. TNFR2 is mainly associated with homeostatic biological activities, including tissue regeneration, and cell proliferation, and also triggers inflammatory responses[104-105]. The relevant mechanism is shown in Fig. 4.

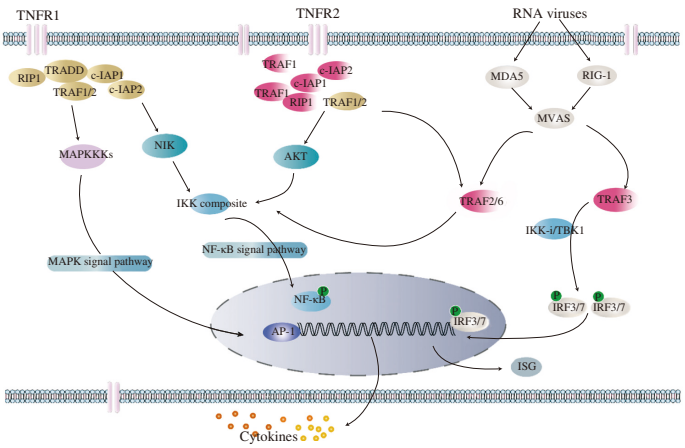

Fig. 4 RIG-I like receptors/TNF signaling pathway.

2.3.4 *Other related signaling pathways*

PI3K-AKT signaling pathway is an intracellular signal transduction pathway, that has various effects such as responding to extracellular signals, promoting glucose metabolism, cell proliferation, cell growth, and angiogenesis. The activation of the PI3K-Akt signaling pathway can mediate the activity of transcription factors including NF-κB, promoting the production of inflammatory factors and cell inflammation[106-107]. Studies have shown that the FOXO signaling pathway plays a key role in a wide range of cellular processes. FOXO transcription activates or represses downstream target genes, which play important roles in proliferation, apoptosis, autophagy, metabolism, and inflammation. FOXO1 can bind to the promoter of IL-1β and enhance the activity of the IL-1β promoter. This effect leads to increased IL-1β expression that can be inhibited by insulin signaling. When PI3K-Akt signaling is reduced, inflammation levels increase because more FOXO1 binds to the promoter sites of inflammatory genes. In addition, FOXO1 amplifies the effect of NF-κB-induced inflammation, and if this amplifying component is suppressed, inflammation is reduced[108-109]. Wang et al.[91] used proteomic techniques to find that Carnosic acid negatively regulated 217 LPS-induced proteins involved in a variety of inflammatory processes, including MAPK, NF-κB, and FOXO signaling pathways.

In the last 3 years, the research of proteomics technology in inflammation has gradually increased, and we summarize the application of proteomics technology in drug target discovery and mechanism research of inflammation, as detailed in Table 3. With the continuous development of omics technology, the use of proteomics technology to find drug targets and mechanisms has become a new trend in targeted drug development.

3. The application of proteomics to inflammatory diseases

Prolonged or repeated inflammation may lead to lesions in tissues or organs, leading to various diseases, such as heart disease, diabetes, cancer, etc. Tissues or organs are important places for the occurrence and development of diseases, in which pathological changes and molecular mechanisms can reflect the characteristics and essence of diseases. Through pathological examination and molecular biological analysis of tissues or organs, providing a deeper understanding of diseases, and accurate strategies for disease prevention, diagnosis, and treatment.

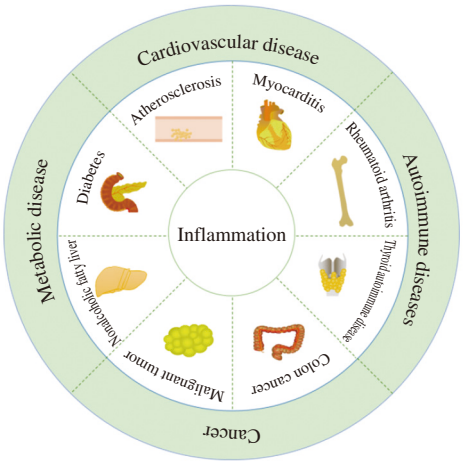

Fig. 5 Inflammation is at the heart of many chronic diseases.

Diabetes mellitus is a serious and common chronic inflammatory disease. Type 2 diabetes mellitus (T2DM) is an endocrine disease caused by insulin resistance and pancreatic β-cell dysfunction. Many studies have found that the expression and secretion of various inflammatory factors in the serum of patients with T2DM are increased, and these inflammatory factors and markers can cause insulin resistance (IR) by interfering with normal insulin signal transduction pathways[128]. PI3K/Akt and Shc/Raf/MAPK signaling pathways are the main signaling pathways regulated by insulin. Tamas et al.[129] discovered through proteomic technology that

Table 3
Application of proteomics techniques to therapeutic targets on inflammation.

Cell types	Control group	Experimental group	Proteomic approach	Potential targets	Signaling pathways	Reference
RAW264.7	LPS	Phillygenin	iTRAQ, LC-MS/MS	GSK-3β, CBP, NIK, RSK1	RIG-I-like receptor/NF-κB/MAPK signaling pathway	[102]
RAW264.7	LPS	Tetramethylpyrazine	TiO_2, LC-MS/MS	TRAF6, NF-κB	TLR4/NF-κB signaling pathway	[110]
RAW264.7	LPS	Artemisinin	LC-MS/MS	HSP90	–	[111]
RAW264.7	LPS	Sinomenine	LFQ, LC-MS/MS	RIPK3, PTGES3, PRDX4, ADH5, UTP18, DDX27, SNX5, MYH11, TRMT2A, PSMD6, NCAPH	NF-κB signaling pathway	[112]
RAW264.7	LPS	Carnosic acid	LC-MS/MS	–	NF-κB/MAPK signaling pathway, FOXO signaling pathway	[91]
RAW264.7	LPS	Arctigenin	TMT, LC-MS/MS	Keratin 14	NF-κB signaling pathway	[113]
RAW264.7	LPS	κ/ι-Carrageenan hexaoses	LFQ, LC-MS/MS	RELA/p65, CREB1, NFAT5	NF-κB/MAPK signaling pathway	[114]
RAW264.7	H1N1	ShuFengJieDu capsule	iTRAQ, LC-MS/MS	–	NF-κB/MAPK signaling pathway	[97]
RAW264.7	H2O2	SEPS-4	2D-GE, MALDI-TOF MS	PRDX2, EEF1G, PEBP1, Enolase 1, PFAS		[115]
RAW264.7	LPS	Tetramethylpyrazine	TiO_2, LC-MS/MS	ITGA4, HSP90α, TRAF, CASP8, AP-1, PTGS2	TLR4/NF-κB signaling pathways	[116]
RAW264.7	LPS	GDF11	TMT, Lip-MS	TGFβR1	NF-κB/MAPK signaling pathway	[117]
THP-1	DMSO	Berberine probes	LC-MS/MS	NIMA-related kinase 7		[118]
THP-1	Dengue virus	PLT	LC-MS/MS	Platelet gactor 4	MAPK signaling pathway, JAK/STAT signaling pathway	[119]
THP-1	S protein	Perindopril	LFQ, Nano-LC-MS/MS	ER oxidoreduclin 1α	TNF signaling pathway, IFN signaling pathway	[120]
THP-1	LPS	Cyclohexane-1,2-dicarboxylic acid diisononyl ester	TMT, LC-MS/MS	–	Toll-like receptor/NF-κB signaling pathway	[121]
THP-1	LPS	1G244	iTRAQ, LC-MS/MS	Dipeptidyl peptidase 8/9	Toll-like receptor/NF-κB signaling pathway	[122]
BV-2	DMSO	Arone	LC-MS/MS	ASF1a	NF-κB signaling pathway	[83]
BV-2	LPS	1,6-*O*,*O*-Diacetylbritannilactone	LC-MS/MS	NLRP3	TLR4/NF-κB/MAPK signaling pathway	[123]
BV-2	LPS/IFNγ	1,2,3,4,6-Penta-*O*-galloyl-*β*-*D*-glucose-purity	LC-MS/MS	Ataxin-2, septin 7, adenylosuccinate synthase	NF-κB/MAPK signaling pathway	[124]
Macrophage	LPS	Nicotinamide mononucleotide	TMT, LC-MS/MS	Cyclooxygenase-2, prostaglandin E2	–	[125]
EA.hy926	*Tert*-butyl hydroperoxide	Crude flavonoids of pollen	iTRAQ, LC-MS/MS	PMPCB, PMPCA, MIPEP, GPX1, PITRM1	NF-κB signaling pathway	[126]
bMECs	Streptococcus agalactiae	Soybean isoflavones	TMT, LC-MS/MS	ITGA5	HIF-1 signaling pathway	[127]

Note: ADH5, alcohol dehydrogenase 5; CBP, CREB binding protein; CREB1, cAMP responsive element binding protein 1; EEF1G, eukaryotic translation elongation factor 1 gamma; GPX1, glutathione peroxidase 1; HIF, hypoxia inducible factor; ITGA, integrin alpha; MIPEP, mitochondrial intermediate peptidase; NCAPH, non-SMC condensin I complex subunit H; NFAT5, nuclear factor of activated T-cells 5; PEBP1, phosphatidylethanolamine-binding protein 1; PFAS, phosphoribosyl formylglycinamidine synthase; PITRM1, pitrilysin metallopeptidase 1; PMPCA, processing peptidase subunit alpha; PMPCB, mitochondrial-processing peptidase subunit beta; PSMD6, 26S proteasome non-ATPase regulatory subunit 6; PTGES3, prostaglandin E synthase 3; RSK1, ribosomal S6 kinase 1; SNX5, sorting nexin 5; TGFβR1, transforming growth factor-beta receptor 1; TRMT2A, tRNA methyltransferase 2 homolog A; UTP18, U3 small nucleolar RNA-associated protein 18.

smoothelin-like 1 (SMTNL1) plays a crucial role in maintaining the physiological ratio of Tyr/Ser IRS1 phosphorylation and attenuating the insulin signaling cascade leading to impaired glucose handling, which makes it a potential therapeutic target for improving insulin resistance. Yang et al.[130] performed proteomic analysis of rat adipose tissue and found that fatty acid-binding protein 4 (FABP4) was highly expressed in insulin-resistant cells. By using FABP4 inhibitors, it was found that inhibition of FABP4 could effectively promote GLUT4 transport. Therefore, effective inhibition of FABP4 can improve insulin resistance. Montgomery et al.[131] performed proteomic analysis of mouse liver and identified aryl sulfonated enzyme A (ARSA) as an up-regulated hepatic factor in nonalcoholic steatohepatitis (NASH) and T2DM. Then, ARSA knockdown mice were constructed through the AAV virus, and the results showed that ARSA is a new target for T2DM.

Atherosclerosis is a chronic inflammatory disease characterized by lipid retention and hardening of blood vessels, which is the beginning of cardiovascular disease[132]. Effectively inhibiting atherosclerosis can reduce inflammation and cardiovascular disease. Cansby et al.[133] conducted proteomics analysis of human aortic smooth muscle cells transfected with serine threonine kinase (STK) 25 siRNA and combined with other molecular biological experiments and found that silencing STK25 can reduce lipid accumulation, inhibit the activation of inflammatory and fibrotic pathways, and reduce oxidation and endoplasmic reticulum stress. This kinase is a new potential therapeutic target for atherosclerotic diseases. Among the above-mentioned therapeutic targets, STK3 is a homologous protein with STK25[134], which suggests that whether we can search for drug targets through homologous proteins is also a new idea.

Chuang et al.[135] used proteomic techniques to analyze the proteins of T cell-derived exosomes in patients with systemic lupus erythematosus and healthy controls. The results showed that bactericidal/permeability-increasing (BPI) protein was a negative regulator of regulatory T-cell differentiation. Overexpression of

BPI protein in T cell-derived exosomes or peripheral blood T cells may be a biomarker and pathogenic factor for human systemic lupus erythematosus nephritis, hepatitis, and arthritis. Ren et al.[136] studied the synovial tissue protein profile of patients with rheumatoid arthritis and osteoarthritis by using TMT proteomics technology and found that olfactomedin 4 (OLFM4) was up-regulated in the synovial tissue samples of rheumatoid arthritis. Knockdown of OLFM4 inhibited the proliferation of fibroblast-like synoviocytes and decreased the expression of CXCL9, CXCL11, and MMP-1 in RA, suggesting that OLFM4 may be a promising therapeutic target for RA. Through proteomic analysis of blood, urine, tissue, and other samples of patients with inflammatory diseases, we can find the proteins and signaling pathways associated with inflammatory diseases, and provide more accurate guidance for the treatment of inflammatory diseases.

4. Challenges and prospects

The continuous progress of science and technology has brought infinite hope for the health and well-being of humanity. This advancement not only helps us better understand and address health issues but also provides numerous new opportunities to improve and extend human life. The proteomics technology assists researchers in gaining a deeper understanding of the complexity of biological systems, the regulation of biological processes, and interactions. Furthermore, the significance of proteins in clinical medicine has become increasingly apparent and continues to expand, including metabolic disorders, cardiovascular diseases, autoimmune diseases, and cancer. Through the analysis of patient tissue samples, it is possible to identify biomarkers associated with diseases, uncover disease mechanisms, and formulate earlier and more precise diagnostic and personalized treatment strategies, thereby advancing research and clinical practices in the field of inflammatory diseases. Therefore, the development of proteomics technologies holds immense potential value in the field of clinical medicine.

Although proteomics has made great achievements, it still faces many challenges. For instance, how to isolate and prepare samples that can objectively reflect proteomics, improve the detection rate of low abundance proteins, and determine the absolute content of proteins, which will limit the development of proteomics. The analysis of proteomic results depends on the enrichment and integration of bioinformatics, and the results need to be verified. Therefore, while utilizing proteomics technology, it is necessary to further verify the target proteins and molecular mechanisms in combination with other molecular biological methods and clinical trials, to more fairly reflect the changes in proteomics and help to translate the basic research results into clinical applications. In addition, proteomics results identify a large number of differential proteins, how to quickly screen the key target proteins and biomarkers is a more critical issue. Therefore, to further improve the detection speed, sensitivity, repeatability, high throughput, and automation level of protein isolation and identification technology and to establish a more perfect protein database and analysis software and a series of related issues will be conducive to the in-depth development of proteomics research.

In the fields of systems biology, biological phenomena and gene expression regulation are complex and diverse. Omics research plays an irreplaceable role in the diagnosis and treatment of diseases. However, the research method of single omics is often limited, which can only describe the regulatory mechanism behind it from a single dimension, and its effectiveness needs to be verified. Only through the mutual promotion and penetration of proteomics and other omics can the nature and law of life phenomena be further revealed, which is of great significance to the protection of human life and health.

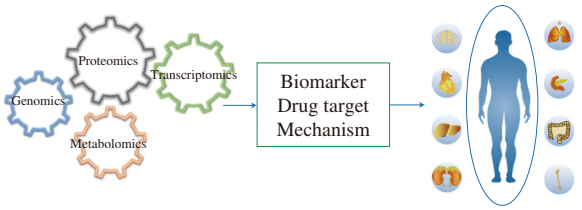

Fig. 6 Application of multi-omics techniques in human health.

Conflict of interest

Wenyi Kang is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors report that there is no conflict of interest.

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