Supplementary information

Pretreatment of the standard proteins and actual sample

β-casein (1 mg) HRP (1 mg) and BSA (2 mg) were dissolved in 100 μL of deionized water, respectively. After 5 minutes of ultrasonic mixing, the proteins were denatured in 100 °C boiling water for 15 minutes. After the denatured protein sample was cooled to room temperature, 100 μL of ammonium bicarbonate (50 mM) was added together with the addition of trypsin at protein to trypsin quality ratio of 40 to1.

The mixed solution was incubated for 16 hours at room temperature to allow complete protein digestion. The obtained solutions were collected in centrifuge tubes and saved at −20 °C for further use. Serum (2 μL) was diluted in 16 μL of NH_4HCO_3 (50 mM) buffer and denatured in 100 °C boiling water for 15 min. The mixture was reduced by DTT at 37 °C for 1 h and alkylated by IAA at 37 °C for 1 h in the dark. Then the obtained mixture was incubated with trypsin (trypsin/protein is 1/40, w/w) at 37 °C for 16 h. Tryptic digests were lyophilized for further enrich and analyze.

Characterization

Scanning electron microscopy (SEM, Keol 2012 microscope), Energy-dispersive X-ray spectroscopy (EDX, Keol 2012 microscope), Fourier transform infrared spectra (FT-IR, Thermo Fisher Scientific 10 infrared spectrometer analysis), XPS (Thermo Scientific K-Alpha).

Mass spectrometry analysis and database search

For MALDI-TOF MS analysis. All the sample analyses were performed on a Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI TOF MS) (Bruker, USA). Firstly, 1 μL of eluent was spotted on the target plate and dried naturally. Next, 1 μL of matrix solution was spotted on the sample target and dried naturally for MS analysis. MALDI-TOF MS spectra were acquired in the positive ion mode with an Nd:Y AG laser (383 nm) at 20 kV of TOF accelerating voltage. The mass to charge (m/z) range from 1000 to 5100 were recorded under the constant laser intensity. The results were analyzed by the FlexAnalysis software.

The experiments were conducted on an EASY-nLCTM 1200 system (Thermo Scientific, USA) coupled with an Orbitrap Fusion Lumos mass spectrometer (Thermo Finnigan, San Jose, CA) with nanoelectrospray ion source. Solvent A (water with 0.1% formic acid) and solvent B (ACN with 0.1% formic acid) were prepared. The deglycosylated peptides (10 μL) were loaded by the autosampler into the trap column (Thermo Scientific, 100 μm × 2 cm, 5 μm, 100 Å, C18), with a flow of 8 μL/min for 4 min and subsequently separated on the analytical column (Thermo Scientific, 75 μm × 25 cm, 5 μm, 100 Å, C18). The relevant liquid gradient was as follows: from 0 min to 40 min, the linear gradient was from 5% B to 28% B; from 40 min to 42 min, thelinear gradient was from 28% B to 90% B, and from 42 min to 60 min, solvent B was kept at 90%. The flow rate was 300 nL/min, and the column temperature was maintained at 40 ℃. The electrospray voltage was operated at 2.0 kV with the ion transfer capillary at 300 °C. The mass spectrometer was run in positive mode. Full-scan MS spectra (m/z 350–1800) were acquired in the Orbitrap with a resolution of 120,000 at m/z 200, scan mode set at top speed, the microscans were set at 1. The AGC target was set to $4e^5$, and the maximum injection time was 50 ms, the number of scan ranges set at 1, dynamic exclusion of 40.0 s, data-dependent mode set at cycle time, and the time between master scans set at 3 s. The mass-to-charge ratios of peptides and peptide fragments were gathered in line with the following strategy: the MS2 scan was performed at the same time as the master scan, the cycle time was 3 s.The intensity threshold was $5e^4$ and the MS2 activation type was HCD, the MS2 resolution was 50,000 at m/z 200. The microscans were set at 1, the maximum injection time was

105 ms, and the AGC target was set to $1e^5$. The isolation window was 1.6 m/z, the HCD collision energy was 35% and first mass was set at 110 m/z.

Database search and data analysis. The original data of mass spectrometry analysis was RAW file, and the built-in software Proteome Discoverer 2.4 (Thermo Scientific) was used for library identification and quantitative analysis. The uniprot database is used this time: uniprot_human_20210621_202249.fasta. When searching the library, submitting the RAW file to SequestHT through Proteome Discoverer, selecting the established database, and then searching the database. The search parameters were as follows: monoisotopic mass, trypsin digestion, maximum 2 missing cut sites, peptides Charged number: 2+, 3+ and 4+, fixed modification to carbamidomethylation (C), dynamic modification to oxidation (M), Acethyl (protein N-term), Deamidated [N] and Phospho (S, T, Y). The maximum error of the precursor ion was 10 ppm, and the maximum error of the fragment ion was 0.05 Da. Proteome Discoverer 2.4 performs Peptide high Confidence screening based on the peptide identification results and outputted the results.

The protocol of actual biological sample analysis with nano-LC-MS/MS

1 mg of hydrazide-POPs-Ti^{4+} was added into 100 μL of loading buffer containing a determined amount of serum digestion. The mixed solution was incubated for 1 h at 37 °C, and removed supernatant by centrifugation. Then, the peptides-loaded hydrazide-POPs-Ti^{4+} was washed with loading buffer for 3 times. Target peptides were eluted with 2 × 10 μL of eluent and used centrifugation to remove the particle to isolate the eluted peptide solution. Afterwards, the eluent was lyophilized and the lyophilized peptides were redissolved in NH_4HCO_3 solution (25 mM) and then lyophilized. The obtained solution was employed for further nano-LC-MS/MS analysis.

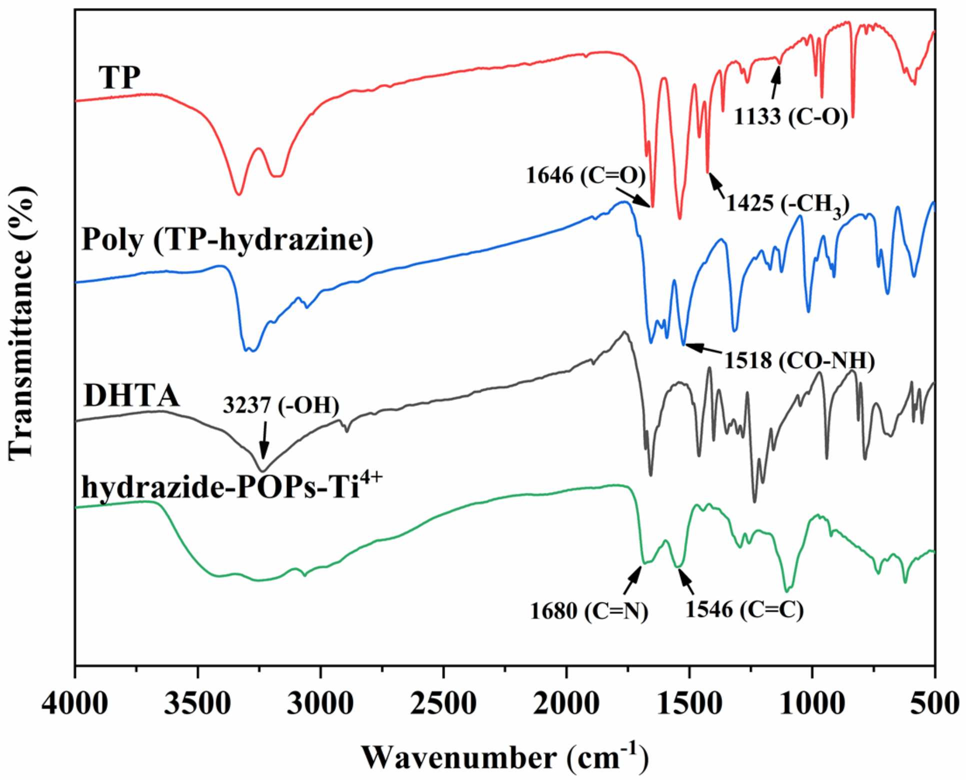

Fig. S1 The FT-IR spectra of TP, Poly (TP-hydrazine), DHTA and hydrazide-POPs-Ti^{4+}.

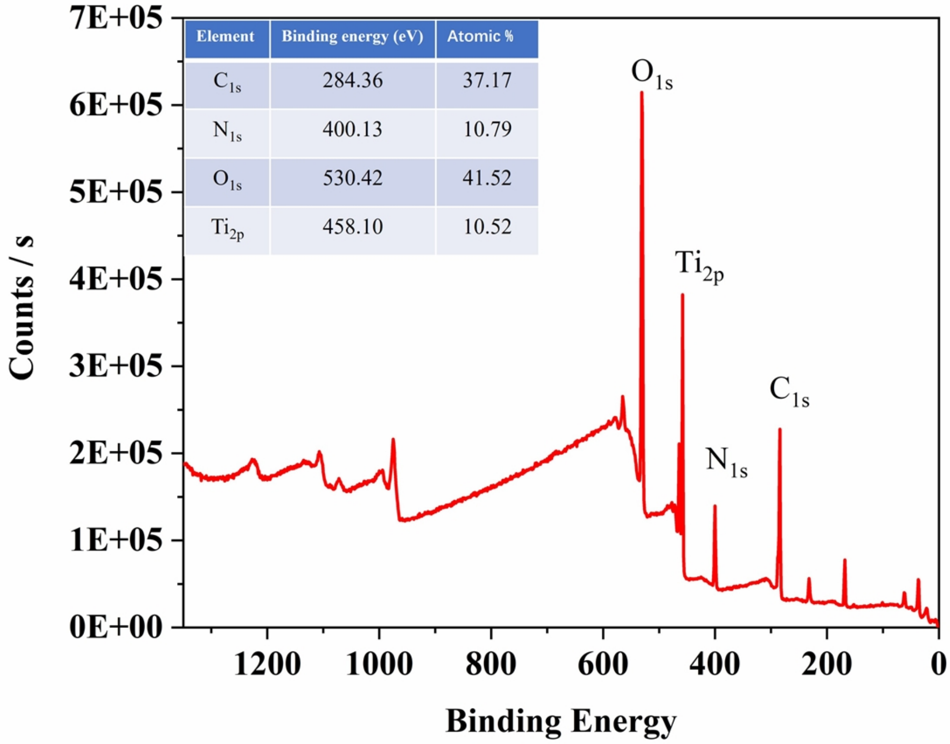

Fig. S2 The XPS spectra of hydrazide-POPs-Ti^{4+}.

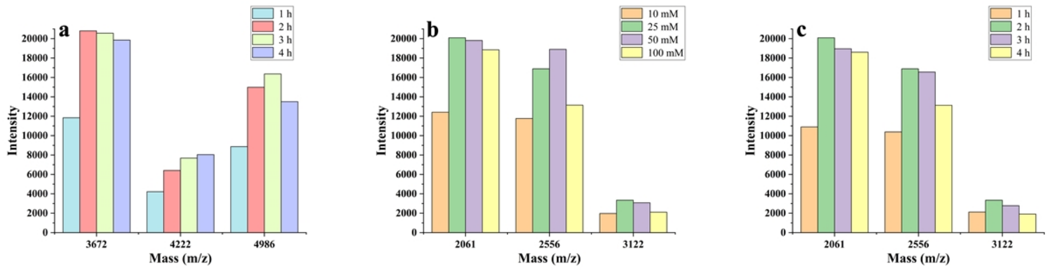

Fig. S3 (a) The enrichment performance of hydrazide-POPs materials prepared at different time. The enrichment performance of hydrazide-POPs-Ti^{4+} materials prepared at different concentrations (b) and time (c).

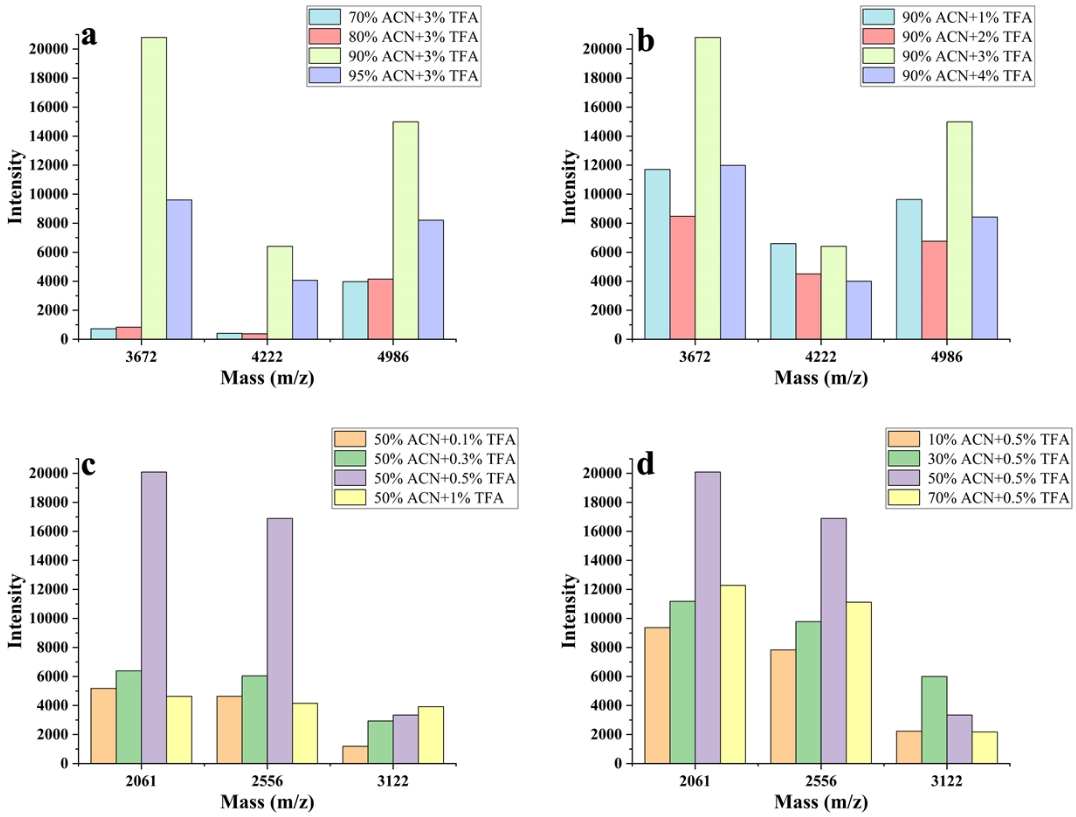

Fig. S4 Optimization of enrichment of glycopeptides (a, b) and phosphopeptides (c, d) by hydrazide-POPs-Ti^{4+} with different loading buffer.

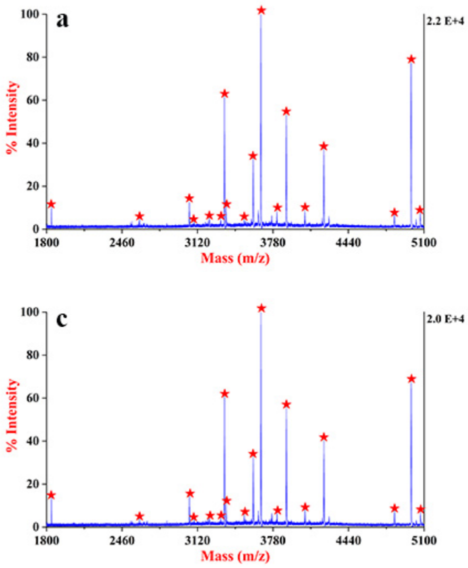

Fig. S5 MS spectra analysis of glycopeptides from HRP digests after enriched by hydrazide-POPs-Ti^{4+}: (a) the first time, (b) the fourth time, (c) the seventh time, and (d) the tenth time. Glycopeptides peaks are marked with "★".

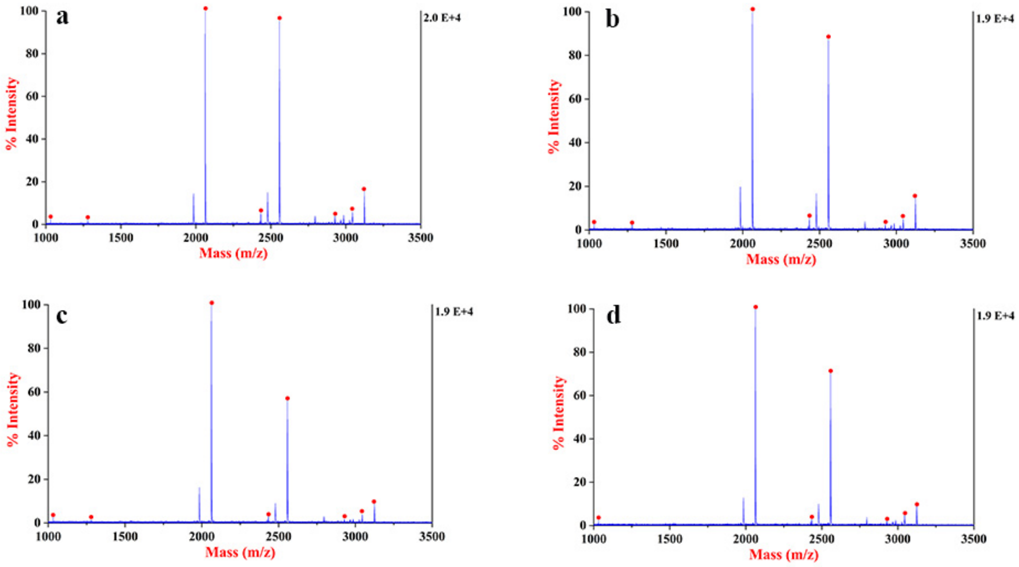

Fig. S6 MS spectra analysis of phosphopeptides from β-casein digests after enriched by hydrazide-POPs-Ti^{4+}: (a) the first time, (b) the fourth time, (c) the seventh time, and (d) the tenth time. Phosphopeptide peaks are marked with "•".

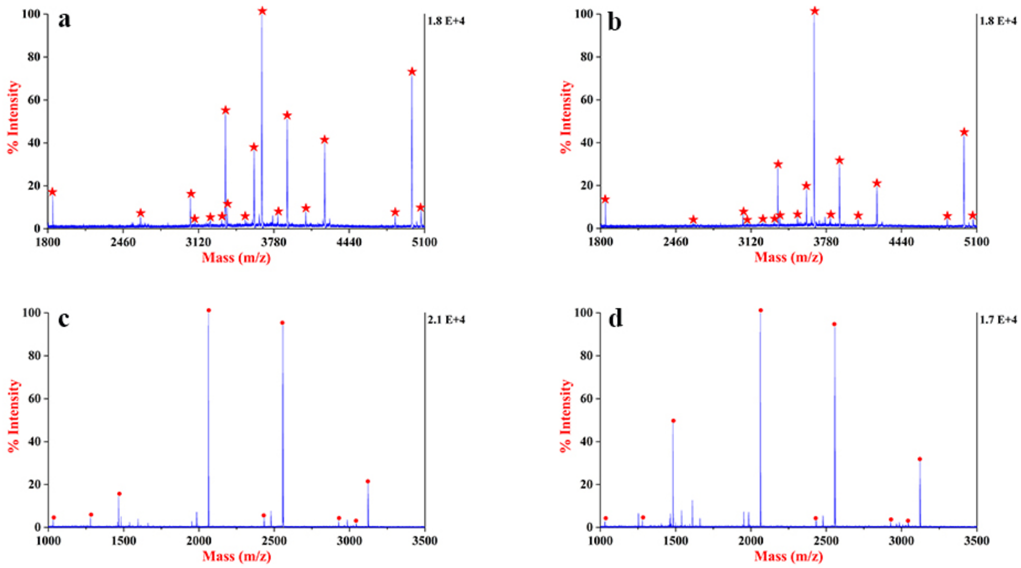

Fig. S7 MS spectra analysis of hydrazide-POPs-Ti^{4+} enriched glycopeptides and phosphopeptides with different pH. pH=3: (a) glycopeptides, (c) phosphopeptides; pH=11: (b) glycopeptides, (d) phosphopeptides. Glycopeptides peaks are marked with "★". Phosphopeptide peaks are marked with "•".

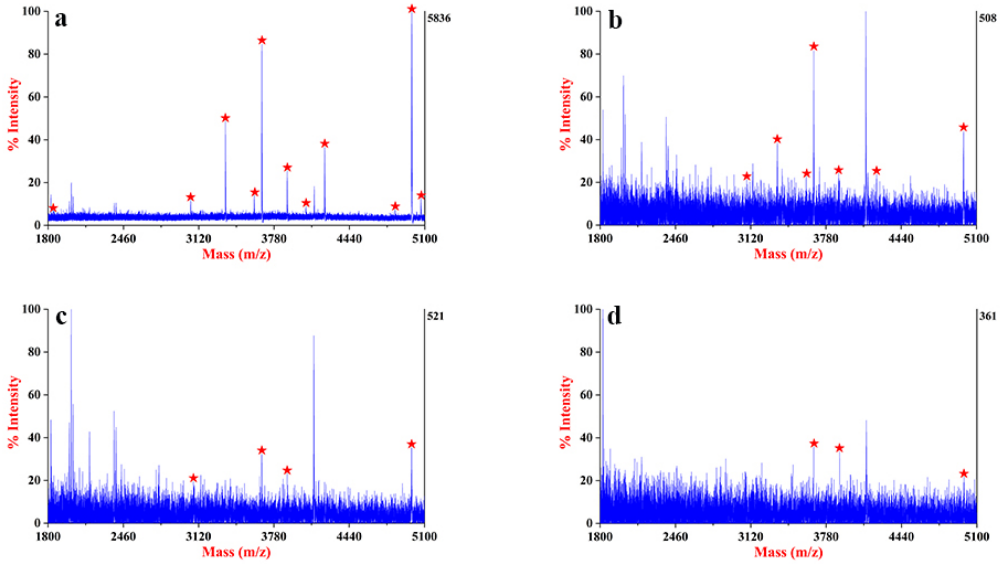

Fig. S8 MS spectra of enriched glycopeptides from a mixture of HRP and BSA with different molar ratio, (a) 1:100, (b) 1:500, (c) 1:1000, (d) 1:2000, glycopeptides peaks are signed as "★".

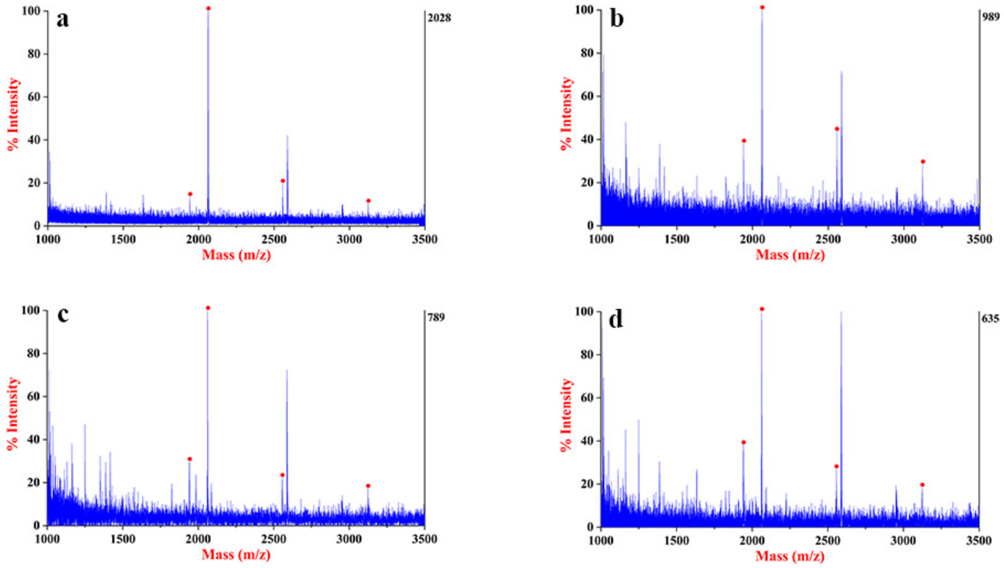

Fig. S9 MS spectra of enriched phosphopeptides from a mixture of *β*-casein and BSA with different molar ratio, (a) 1:100, (b) 1:250, (c) 1:500, (d) 1:1000, phosphopeptides peaks are signed as "•".

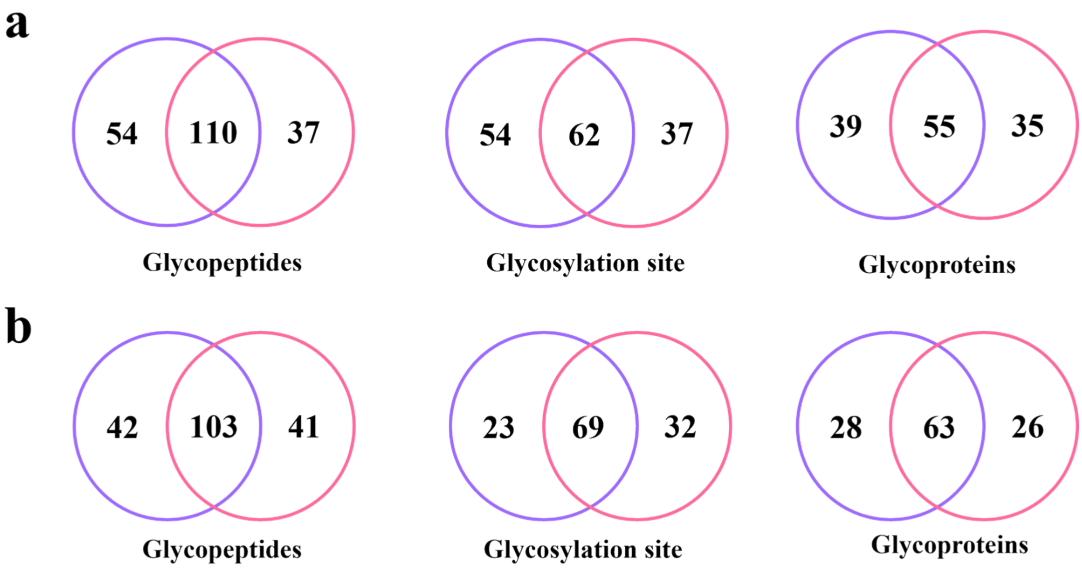

Fig. S10 Venn diagram of glycopeptides, glycosylation sites, and glycoproteins of (a) normal controls and (b) breast cancer patients.

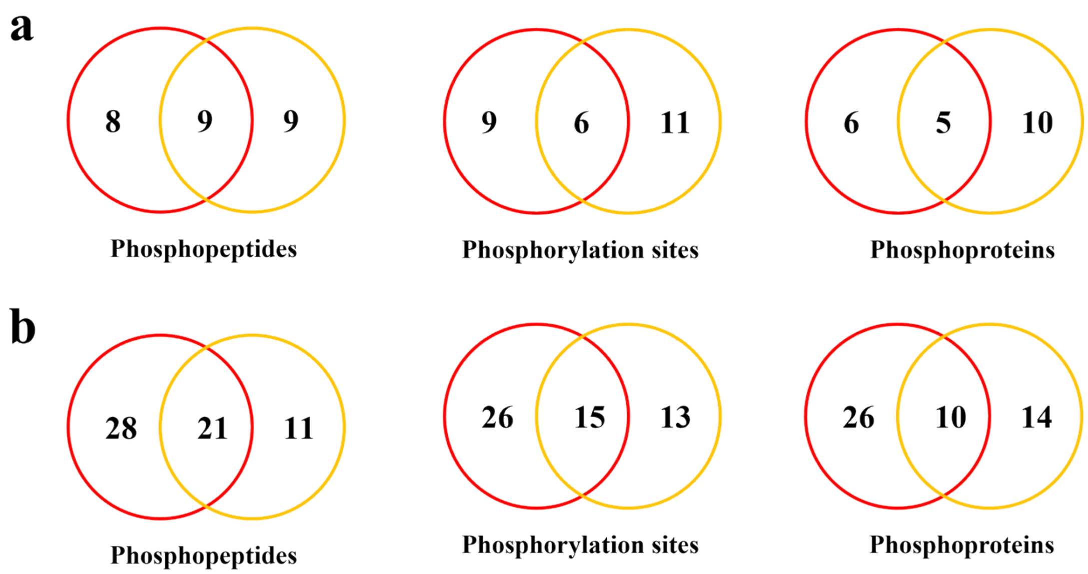

Fig. S11 Venn diagram of phosphopeptids, phosphorylation sites, and phosphoproteins of (a) normal controls and (b) breast cancer patients.

Table S1 The detailed information of glycopeptides derived from HRP after enrichment by hydrazide-POPs-Ti^{4+} composites.

No.	m/z	Sequence Glycan composition	Amino acid sequence
1	1842	$XylMan_3FucGlcNAc_2$	NVGLN#R
2	2544	XylMan3FucGlcNAc2	SSPN#ATDTIPLVR
3	2591	XylMan3FucGlcNAc2	PTLN#TTYLQTLR
4	2612	XylMan3GlcNAc2	MGN#ITPLTGTQGQIR
5	3048	XylMan2GlcNAc2	SFAN#STQTFFNAFVEAMDR
6	3088	XylMan3FucGlcNAc2	GLCPLNGN#LSALVDFDLR
7	3323	XylMan3FucGlcNAc2	QLTPTFYDNSCPN#VSNIVR
8	3354	XylMan3FucGlcNAc2	SFAN#STQTFFNAFVEAMDR
9	3369	XylMan3FucGlcNAc2	SFAN#STQTFFNAFVEAM*DR
10	3540	Man3FucGlcNAc2	GLIQSDQELFSSPN#ATDTIPLVR
11	3606	XylMan3FucGlcNAc2	NQCRGLCPLNGN#LSALVDFDLR
12	3672	XylMan3FucGlcNAc2	GLIQSDQELFSSPN#ATDTIPLVR
13	3895	XylMan3FucGlcNAc2	LHFHDCFVNGCDASILLDN#TTSFR
14	4057	XylMan3GlcNAc2	QLTPTFYDNSC(AAVESACPR)PN#VSNIVR-H2O
15	4223	XylMan3FucGlcNAc2	QLTPTFYDNSC(AAVESACPR)PN#VSNIVR
16	4720	Man3FucGlcNAc2, Man3FucGlcNAc2	LYN#FSNTGLPDPTLN#TTYLQTLR

17	4823	XylMan2FucGlcNAc2, XylMan2GlcNAc2	LYN#FSNTGLPDPTLN#TTYLQTLR
18	4838	XylMan3FucGlcNAc2, XylMan3GlcNAc2	LYN#FSNTGLPDPTLN#TTYLQTLR
19	4854	Man3FucGlcNAc2, XylMan3FucGlcNAc2	LYN#FSNTGLPDPTLN#TTYLQTLR
20	4985	XylMan3FucGlcNAc2, XylMan3FucGlcNAc2	LYN#FSNTGLPDPTLN#TTYLQTLR
21	5068	Xyl Man3GlcNAc2	QLTPTFYDNSC(AAVESACPR)PN#V SNIVR

Table S2 The detailed information of phosphopeptides derived from *β*-casein after enrichment by hydrazide-POPs-Ti^{4+}.

No.	**m/z**	**Amino acid sequence**	**Numbers of Phosphorylation site**
1	1030.9	FQ[pS]EEQQQTEDELQDK	1
2	1539.4	EQL[pS]T[pS]EENSKK	2
3	1562.1	RELEELNVPGEIVESL[pS][pS][pS]EE[pS]ITR	4
4	1926.7	DIG[pS]E[pS]TEDQAMEDIK	2
5	1942.7	DIG[pS]E[pS]TEDQA[Mo]EDIKa	2
6	2061.9	FQ[pS]EEQQQTEDELQDK	1
7	2925.7	RELEELNVPGEIVE[pS]L[pS][pS][pS]EESITR	4
8	2966.0	ELEELNVPGEIVE[pS]L[pS][pS][pS]EESITR	4
9	3007.3	NANEEEYSIG[pS][pS][pS]EE[pS]AEVATEEVK	4
10	3042.3	RELEELNVPGEIVESL[pS][pS][pS]EESITR	3
11	3122.5	RELEELNVPGEIVE[pS]L[pS][pS][pS]EESITR	4

Table S3 Comparison with other materials that have been used to enrich glycopeptides and phosphopeptides in recent years.

Materials	Number (glycopeptides/ phosphopeptides)	Selectivity (glycopeptides/ phosphopeptides)	LOD (glycopeptides/ phosphopeptides)	Reusability (glycopeptides/ phosphopeptides)	Reference
Fe_3O_4@PDA@mTiO_2@PEI-g-ZIF-8	11 (HRP)/ 7 (β-casein)	1:1000/1:1000	0.04/0.04 fmol/μL	5/5 cycles	1
Fe_3O_4@MIL-100(Fe)	22 (HRP)/ 11 (β-casein)	1:20/1:50	0.1/0.1 fmol/μL	6/6 cycles	2
Fe_3O_4@ILI-01@Ti^{4+}	25 (HRP)/ 11 (β-casein)	1:100/1:1000	2/0.08 fmol/μL	5/5 cycles	3
mMIL-125@Au@L-Cys	26 (HRP)/ 12 (β-casein)	1:100/1:100	0.1/0.1 fmol/μL	5/5 cycles	4
HHZr-MOFs	22 (HRP)/ 3 (β-casein)	1:1000/1:2000	0.5/0.1 fmol/μL	/	5
hydrazide-POPs-Ti^{4+}	18 (HRP)/ 9 (β-casein)	1:2000/ 1:1000	0.1/0.005 fmol/μL	10/10 cycles	This work

'/' not given

Table S4 Details of enriched glycopeptides derived from serum of the breast cancer patients and healthy people by hydrazide-POPs-Ti^{4+} composites. n: N-glycosylation site.

No.	Amino acid Sequence	Protein Group Accessions	MH+[Da]
Glycopeptides were detected in the serum of both normal subjects and breast cancer patients			
1	FSLLGHASISCTVEnETIGVWRPSPPTCEK	P04003; B4E1D8	3373.61914
2	ADTHDEILEGLNFnLTEIPEAQIHEGFQELLR	P01009	3692.80786
3	VDKDLQSLEDILHQVEnK	A0A140VJJ6	2124.0819
4	ELHHLQEQnVSNAFLDKGEFYIGSK	A5PL27	2904.41626
5	LGHCPDPVLVNGEFSSSGPVnVSDK	P20851	2613.21372
6	FnLTETSEAEIHQSFQHLLR	A0A024R6P0	2401.17826
7	LSLHRPALEDLLLGSEAnLTCTLTGLR	Q9NPP6; Q96K68; A0A286YEY5	2964.58228
8	QLVEIEKVVLHPnYSQVDIGLIK	P00738	2635.47053
9	MVSHHnLTTGATLINEQWLLTTAK	P00739; P00738	2680.37631
10	DIAPTLTLYVGKKQLVEIEKVVLHPnYSQVDIGLIK	P00738	4035.27803
11	DTAVFECLPQHAMFGNDTITCTTHGnWTK	D9IWP9	3354.45002
12	AALAAFNAQNnGSNFQLEEISR	P02765	2366.13713
13	VVLHPnYSQVDIGLIK	P00738	1795.99526
14	SQILEGLGFnLTELSESDVHR	P29622	2345.16195
15	EGYSnISYIVVNHQGISSR	P49908	2124.03562

16	SLGNVnFTVSAEALESQELCGTEVPSVPEHGR	P01023	3414.6118
17	LPTQnITFQTESSVAEQEAEFQSPK	B7ZKJ8	2810.33667
18	ADGTVNQIEGEATPVnLTEPAK	C9JF17	2255.10376
19	ADTHDEILEGLNFnLTEIPEAQIH	G3V387	2720.30498
20	LSDLSInSTECLHVHCR	P05156; Q6LAM1	2041.94299
21	ELHHLQEQnVSNAFLDK	A5PL27	2022.98794
22	SVQEIQATFFYFTPnKTEDTIFLR	P02763; P19652	2896.44035
23	VSnQTLSLFFTVLQDVPVR	P01023	2164.16485
24	LSHNELADSGIPGNSFnVSSLVELDLSYNK	A0A384N669	3220.56444
25	LDAPTNLQFVnETDSTVLVR	A0A024R462	2233.13467
26	LGSFEGLVnLTFIHLQHNR	A0A384N669	2196.15601
27	VIDFnCTTSSVSSALANTK	B2R8I2; P04196	2015.95901
28	AFEnVTDLQWLILDHNLLENSK	A0A384N669	2613.31951
29	DIVEYYnDSNGSHVLQGR	A0A140VK00	2066.94139
30	VGQLQLSHnLSLVILVPQNLK	Q5UGI6	2314.34929
31	AVnITSENLIDDVVSLIR	A0A024R035	1972.05971
32	AGLQAFFQVQECnK	A5PL27	1640.77372
33	SPYYnVSDEISFHCYDGYTLR	B4E1Z4	2587.1082
34	MLnTSSLLEQLNEQFNWVSR	A0A384NKS6	2410.17074
35	HYTnSSQDVTVPCR	A0A286YEY5	1664.73331
36	NPPMGGNVVIFDTVITNQEEPYQnHSGR	X6RLJ0	3114.45854
37	FEVDSPVYnATWSASLK	C0JYY2	1914.91199
38	EEQFnSTFRVVSVLTVVHQDWLNGK	Q6N093	2934.46321

39	LEPVHLQLQCMSQEQLAQVAAnATK	Q96PD5	2808.40187
40	EEQYnSTYRVVSVLTVLHQDWLNGK	Q7Z351	2980.46869
41	QEPERnECFLQHK	P02768; F6KPG5	1715.78059
42	KVCQDCPLLAPLnDTR	P02765	1900.92554
43	LHINHNnLTESVGPLPK	A0A384N669	1883.99739
44	NnATVHEQVGGPSLTSDLQAQSK	D9ZGG2	2383.13719
45	FSDGLESnSSTQFEVK	F5GXS0; B7Z1F8; A0A140TA32	1775.79702
46	QNQCFYnSSYLNVQR	P19652	1921.84974
47	QVLFLDTVYGnCSTHFTVK	C0JYY2	2230.08488
48	GLTFQQnASSMCVPDQDTAIR	P01871	2340.05947
49	QQQHLFGSnVTDCSGnFCLFR	P02787	2516.10815
50	SRPAnHCVYFYGDEISFSCHETSR	P04003; B4E1D8	2920.24135
51	EHEGAIYPDnTTDFQR	A5PL27	1893.82496
52	NLFLNHSEnATAK	P00739; P00738	1461.68562
53	VCQDCPLLAPLnDTR	P02765	1772.83058
54	VTQVYAEnGTVLQGSTVASVYK	P27169	2315.17653
55	YTGnASALFILPDQDK	A0A024R6P0	1753.86431
56	LYLGSNnLTALHPALFQNLSK	P22792	2316.22342
57	GGSSGWSGGLAQnR	A0A8Q3WKN4	1334.60837
58	HAnWTLTPLK	P27169	1181.63133
59	LSLLEEPGnGTFTVILNQLTSR	P01833	2403.27658
60	WFSAGLASnSSWLR	Q5SQ11	1582.76487
61	FnSSYLQGTNQITGR	C0JYY2	1686.80819
62	TVLTPATNHMGnVTFTIPANR	P01024	2256.14413

63	LNAENnATFYFK	B4E1C2	1432.67432
64	QVFPGLnYCTSGAYSnASSTDSASYYPLTGDTR	C0JYY2	3552.53836
65	TELFSSSCPGGIMLnETGQGYQR	A0A1U9X793	2533.13336
66	QSVPAHFVALnGSK	F2Z3N2; B4E1Z4	1455.75905
67	YLGnATAIFFLPDEGK	P01009	1756.87923
68	AFITnFSMIIDGMTYPGIIK	B7ZKJ8	2233.12833
69	ALGFEnATQALGR	Q08380	1348.68555
70	VSnVSCQASVSR	P55058	1294.60559
71	LQNNENnISCVER	P36980; B1AKG0	1590.71766
72	LGACnDTLQQLMEVFK	P01008	1867.89285
73	ISEEnETTCYMGK	A0A024R962	1562.6349
74	VYKPSAGnNSLYR	D9IWP9	1470.72233
75	SPDVInGSPISQK	A0A024R962	1342.68489
76	YKnNSDISSTR	P01871	1285.60188
77	LAnLTQGEDQYYLR	A0A384NKS6	1684.81769
78	YAEDKFnETTEK	P43652	1475.65365
79	CIQAnYSLMENGK	C9JF17	1528.67704
80	MDGASnVTCINSR	A0A024R962	1425.60969
81	nTTCQDLQIEVTVK	F5GXS0; A0A140TA32	1649.80508
82	nCCNTENPPGCYR	P43652	1642.60429
83	ANQQLnFTEAK	Q9Y5Y7	1264.61681
84	IDSTGnVTNELR	B4DZ36	1319.64375
85	FSGSGSGTDFnLTISR	A0A5C2FVK9	1646.76566
86	AnLSSQALR	B7Z539	960.51089
87	EVFVHPnYSK	Q8J009	1220.59461
88	YDFnSSMLYSTAK	C0JYY2	1527.66719

89	SWPAVGnCSSALR	P02790	1405.65287
90	nLTTSLTESVDR	P80108	1336.65907
91	AAIPSALDTnSSK	Q08380	1275.64269
92	CGLVPVLAENYNK	P02787	1477.73554
93	ITYSIVQTnCSK	B4E1C2	1414.68826
94	EnISDPTSPLR	D6RHJ6	1229.60082
95	FLNnGTCTAEGK	P05156; Q6LAM1	1312.58379
96	LQnLTLPTnASIK	Q13201	1414.77879
97	AGPnGTLFVADAYK	H0Y512	1424.70562
98	KLPPGLLAnFTLLR	P02750	1553.94138
99	EEQFnSTYR	A0A286YFJ8	1174.50111
100	CGnCSLTTLK	P49908	1154.51802
101	IGGIWTWVGTnK	P14151	1332.69466
102	EEQFnSTFR	Q6N093	1158.50619
103	DAGVVCTnETR	Q08380	1222.53684
104	VELEDFNGnR	Q6UY50	1193.54331
105	ELLETVVnR	K7ER74	1073.58372
106	LGnWSAMPSCK	D9IWP9	1251.54966
107	nFTENDLLVR	P00734	1221.61099
108	nLSMPLLPADFHK	P05546	1483.76136
109	DIENFnSTQK	P43652	1196.54297
110	EEQYnSTFR	A0A4W9A917	1174.50111
111	EGHFYYnISEVK	P55058	1486.68489
112	FGCEIENnR	A0A140VK00	1140.46261
113	CFLGnGTGYR	D6RAR4	1145.50442
114	YNSQnQSNNQFVLYR	B4E1C2	1876.84603

115	EEQYnSTYR	Q7Z351	1190.49602
116	EDALnETR	A0A384NKS6	948.42688
117	LDVDQALnR	I3L145	1044.53201
118	IGEADFnR	P04275	922.42649
119	DFYVDEnTTVR	P29622	1359.6063
120	EWDnTTTECR	P20851	1312.51102
121	GAFISnFSMTVDGK	P19823	1474.68826
122	nECFLQHK	P02768; F6KPG5	1076.48296
123	LPPGLLAnFTLLR	P02750	1425.84641
124	GLnVTLSSTGR	F5GXS0; A0A140TA32	1105.58478
125	DTFVnASR	Q5UGI6	910.42649
126	THTNISESHPnATFSAVGEASICED DWNSGER	P01871	3520.48297
127	EEQFnSTFRVVSVLTVVHQDWLN GKEYK	Q6N093	3353.68008
128	THTnISESHPnATFSAVGEASICED DDWSGER	P0DOX6	3521.46699
129	LAGKPTHVnVSVVMAEVDGTCY	Q96DK0; Q9NPP6; Q96K68	2348.12609
130	ALPQPQnVTSLLGCTH	P02790	1736.8636
131	NPVGLIGAEnATGETDPSHSK	A0A5F9ZH15	2094.99382
132	VLAEAMSHAnSSIMMQRGNFR	A0A5J6A018	2368.08425
133	TLnQSSDELQLSMGNAMFVK	A0A024R6P0	2214.0417
134	nNSDISSTR	P01871	994.44359
135	VTISCSGnSSNIGR	A0A5C2GGK1	1453.65875
136	FnDTEVLQR	A0A5F9ZH15	1122.54258
137	GLCVnASAVSR	A6XND1	1134.55718

138	TMFPnLTDVR	F2Z3N2; B4E1Z4	1194.58234
139	nGTLVAFR	Q92954	878.47304
140	GVnVCQETCTK	A8K9A9	1296.55586
141	LNVEAAnWTVR	P80108	1273.65353
142	MFSQnDTR	P02750	999.42002
143	CnECGKAFSTK	Q92970	1302.5453
Glycopeptides detected only in normal serum			
1	QLVEIEKVVLHPnYSQVDIGLIKLK	P00738	2876.64956
2	GLKFnLTETSEAEIHQSFQHLLR	A0A024R6P0	2699.37875
3	LGACnDTLQQLMEVFKFDTISEK	P01008	2688.28953
4	ADGTVNQIEGEATPVnLTEPAKLEVK	C9JF17	2724.3938
5	nGTGHGNSTHHGPEYMR	P02790	1853.76198
6	FVEGSHnSTVSLTTK	C0JYY2	1607.79114
7	IGPGQTFYAVGDIIGDIRQAHCNISEKDWnKTLEDVK	A0A286LHX8	4189.06588
8	SRYPHKPEInSTTHPGADLQENFCR	P00734	2955.38023
9	QGFGNVATNTDGKnYCGLPGEYWLGNDK	P02675	3076.37414
10	nECFLQHKDDNPNLPR	P02768; F6KPG5	1997.9134
11	TERPLSSGVYMGnLSAQQLEQRRSLLNMIGMVGGAQGTQPGR	A0A3G2CH15	4521.23952
12	GLnVTLSSTGRNGFK	F5GXS0; A0A140TA32	1552.79656
13	KLHINHNnLTESVGPLPK	A0A384N669	2012.09235
14	IYSnHSALESLALIPLQAPLK	P55058	2279.26456
15	DQCIVDDITYNVnDTFHK	A0A024R462	2197.97064
16	YTAFTIPSINnKTPEIRYQYNVLPQ	A0A290DUA5	3344.68377

	GWK		
17	LQAILGVPWKDKnCTSR	Q86U78	1987.04296
18	VTQVYAEnGTVLQGSTVASVYKGK	P27169	2500.29296
19	RNPPMGGNVVIFDTVITNQEEPYQnHSGR	X6RLJ0	3270.55965
20	AATCINPLnGSVCERPAnHSAK	B4DZ36	2369.09725
21	KEHETCLAPELYNGnYSTTQK	P05160	2485.11876
22	GTAGNALMDGASQLMGEnR	P02675	1893.84294
23	nVSCPQLEVPVCPSGFQLSCK	P04275	2407.10906
24	STGKPTLYnVSLVMSDTAGTCY	P01871	2366.08904
25	AKVGQLQLSHnLSLVILVPQNLK	Q5UGI6	2513.48137
26	ESPNNAKTIIVHLnESVEInCTRPSnNTRTSITMGPGHVFYR	Q8Q6G7	4755.33659
27	nYSTQAGATQAGRFSITPAAPSYTLKLGEYGEVTVDCEPR	B3F776	4307.05611
28	DnCCILDER	A0A140VJJ6	1195.4718
29	nHSCEPCQTLAVR	Q8IZZ5	1572.68934
30	CATPHGDnASLEATFVK	P23142	1818.83269
31	DLQSLEDILHQVEnK	A0A140VJJ6	1781.89158
32	EVYPWYnLTVEAK	Q59EA3	1612.78935
33	WSDIWnATK	F8WF14	1121.5262
34	LIIYnASNR	A0A5C2GHF1	1064.57349
35	KDWnDTLQnVTEK	Q9J0Z8	1592.74386
36	FGYILHTDnR	P48740	1236.60076
37	FnGSGSGTDFTLK	A0A5C2G3W4	1331.61139
38	EDGGGWWYnR	P02675	1240.50178

39	LDASISnnSTSKRK	P12757	1521.78673
40	SLGNVnFTVSAEALESQELCGTEVPSVPEHGRK	P01023	3542.70677
41	ICDLLVANNHFAHFFAPQnLTNMNK	B7Z539	2931.39164
42	NCGVnCSGDVFTALIGEIASPNYPKPYPENSR	P09871	3527.62059
43	QQQHLFGSnVTDCSGnFCLFRSETKDLLFRDDTVCLAK	B4E1B2; P02787	4509.09079
44	LATALSLSNKFVEGSHnSTVSLTTK	C0JYY2	2606.36719
45	LQAPLnYTEFQKPICLPSK	A8K9A9	2248.16822
46	HQDFNSAVQLVEnFCR	P00734	1964.89194
47	QIVNMWQGTGQAMYAPPIRGPINCVSnITGILLTRDGGDNNR	K4NYZ3	4632.23919
48	CVPTDPNPQEIRLEnVTENFNMWK	F5B6A0	2933.34442
49	IYSGILnLSDITK	A8K9A9	1437.78354
50	AELSnHTRPVILVPGCLGNQLEAK	A0A140VK24	2618.36066
51	LETTVnYTDSQRPICLPSK	P03951	2223.09617
52	NIYNYGGDISKMQMGIPDDTYYENVYQEPnVTR	Q8NCR3	3904.73166
53	nHSCSEGQISIFR	B4DZ36	1535.69072
54	FSGSGSGTEFnLTISR	A0A5C2FXG6	1660.78131
55	FSGSTSGnTTTLTISR	Q5NV75	1630.79187
56	AQLLQGLGFnLTER	B2R9F2	1560.83803
57	AFGSNPnLTK	P22792	1049.5262
58	GHTLTLnFTR	A0A024RDY3	1160.60585
Glycopeptides detected only in breast cancer serum			

1	NEEYnKSVQEIQATFFYFTPnKTEDTIFLR	P02763; P19652	3674.7537
2	FQSPAGTEALFELHnISVADSAnYSCVYVDLKPPFGGSAPSER	P04217	4630.17186
3	YPHKPEInSTTHPGADLQEnFCR	P00734	2712.24709
4	CSDGWSFDATTLDDnGTMLFFK	P02790	2529.05847
5	LTPLCVTLnCTTYnRTNGGnTTVEPTMKEEVKnCSFnATTELK	L7WIR7	4908.31584
6	TNVnVTSInNTIMGEMKnCSFnTTTEIR	A0A1W6IAN5	3191.46534
7	SLTFnETYQDISELVYGAK	P01008	2179.04412
8	HGIQYFNnNTQHSSLFTLNEVK	B4E1C2	2593.23176
9	RTNWnVTFDNAAGGDLEVTTHSFNCR	Q5IL01	2985.30679
10	CGnCSLTTLKDEDFCK	P49908	1948.80853
11	GLnLTEDTYKPR	B4DVE1	1407.71144
12	DQYVEPEnVTIQCDSGYGVVGPQSITCSGNR	P04003	3430.51619
13	DCDPPGNPVHGYFEGNnFTLGSTISYYCEDR	P20851	3583.4689
14	GLEWVSSInGSNGR	A0A5C2GE75	1476.70775
15	QDQCIYnTTYLNVQR	P02763	1916.8807
16	CGLVPVLAENYnKSDNCEDT	B4E1B2; P02787	1477.73554
17	FSGSGSDTnFTLTISR	A0A5C2GWP7	1690.79187
18	FQLLnFSSSELK	X5D8W0	1413.72602
19	GRFnISR	A0A7S5C2E9	850.45298
20	CInQSICEK	B4DZ36	1152.50237
21	VELEDFNGnRTFAHY	Q6UY50	1194.52732

22	FGYILHTDnRTCRVE	P48740	1236.60076
23	WEYCnLTR	A0A8J8ZCA0	1142.49352
24	FTDSEnVCQER	P43652	1385.56378
25	TLFCnASK	P20851	941.43969
26	GLINCLSnITGILLTRDGGPSnDSnKTnKTEVFRPGGGDMR	T1RLZ8	4378.14019
27	ESVTDHVNLITPLEKPLQnFTLCFR	P02743	2973.50263
28	SQQKTQQAEAAGGKVSQNYPIVQNLQGQMVHQnLSPR	C3VAH6	4081.99959
29	LGTSLSSGHVLMnGTLK	P80108	1715.89965
30	KYQEKDInASEnGSVMDEANLESLNK	Q9Y6L6	2927.35749
31	DVDKEFYLFPTVFDEnESLLLEDNIR	A5PL27	3161.52012
32	LTPLCVTLnCTNATASnATASnSSIIEGMKnCSFnITTELRDR	M4M317	4747.24301
33	GGNSNGALCHFPFLYNNHnYTDCTSEGR	A0A024R462	3204.31704
34	DGGKGnKTNnNTETFRPGGGNMKDNWR	E7DV11	2983.33473
35	GLEWIGEIYHSGSINYnPSLK	A0A7S5BXW1	2379.15032
36	ELPGVCnETMMALWEECKPCLK	A0A384NKS6	2696.1897
37	EnLTAPGSDSAVFFEQGTTR	A5PL27	2127.98292
38	HGIQYFNnNTQHSSLFMLNEVK	B4DPP8	2622.24055
39	YnWSFIHCPACQCNGHSK	B4DZ36	2267.90555
40	FSGSGSGTDFTLnISR	A0A5C2GL91	1646.76566
41	nASVPNLRGSEK	B3KPT5	1273.63827
42	KESGWSGYPHTQEnVSK	Q8ND71	1934.8879

43	ISnFTNKNMKEVK	H0YNF7	1553.7992

Table S5 Details of enriched phosphopeptides derived from serum of the breast cancer patients and healthy people by hydrazide-POPs-Ti^{4+} composites. s, t, y: Phosphorylation site.

Number	Amino acid Sequence	Protein Group Accessions	MH+[Da]
Phosphopeptides were detected in the serum of both normal subjects and breast cancer patients			
1	VREsDEETQIK	C0JYY2	1413.62573
2	VTEPISAEsGEQVER	U5LGW0	1710.7582
3	TCVADEsAENCDK	P02768	1578.54478
4	ETTCSKEsNEELTESCETKK	B4E1C2	2469.99971
5	ETTCSKEsNEELTESCETK	B4E1C2	2341.90474
6	CDSSPDsAEDVR	P02765	1417.49373
7	CDSSPDsAEDVRK	P02765	1545.58869
8	EsNEELTESCETK	B4E1C2	1635.60915
9	sKEQLTPLIK	V9GYM3	1236.65993
10	DIHVTQsPSSVSASVGDR	A0A5C2GH73	1921.86513
11	AFYTGEIIGDIRQAHCNLsRtK	B2YR04	2710.22083
Phosphopeptides detected only in normal serum			
1	MADEAGsEADHEGTHSTK	P02671	1952.73279
2	NPSSAGsWNSGSSGPGSTGNR	P02671	2043.81521
3	HRHPDEAAFFDTAsTGK	P02671	1966.84433
4	GSESGIFtNTK	P02671	1220.51947

5	LPFLAHALyVQAPTVTIEGFLQALSLAVDK	Q15645	3305.75853
6	VIPMtQSPSSLSASVGDR	A0A5C2FVT6	1953.89873
7	QAHCsIDER	A0A1L7E2S8	1195.45616
8	tDIFVTSFGPVSDHDMEYTIDVF	E5RJS3	2875.08985
9	AGAADsAPYPGGGGNGASGGGSGGSK	A0A8V8TM73	2143.86764
10	FSHsACYYDANQSMYVFGGCTQSSCNAAFNDLWRLDLNSK	Q6P3S6	4924.90032
11	MNNMSFAVPMGsRPCALGLFCCCSSCFCLCCPR	O36595	4199.52446
12	tEGNSTLILPCR	A0A7T3QXW6	1440.65526
13	DDtEQGGGGAGGGNNSGSGAEENSNAAAAAMQPVEDMNDYAIR	A0A7D6TSN7	4267.66843
14	sVLIGEFLEK	Q05DQ2	1214.60683
15	GHEtEMHNIWATHACVPTDPNPQEILMENVTENFNMWK	A0A0H4LWX2	4776.90943
Phosphopeptides detected only in breast cancer serum			
1	LPTDsELAPR	P49908	1178.5453
2	KQLGAGsIEECAAK	B2R7F8	1541.70293

3	KyFIDFVARETTCSKESNEELTESCETK	B4E1C2	3561.48384
4	KATEDEGsEQKIPEATNR	A0A3S8NFS6	2082.93393
5	HTFMGVVSLGSPsGEVSHPR	P02765	2160.98961
6	LGAGtQVIVELGAYVQAESISK	Q6WB99	2313.17377
7	VHtECCHGDLLECADDR	B4DPR2; F6KPG5; A8K9P0	2166.80386
8	YKVDYESQSTDTQNFsSESK	A6XND1	2422.99224
9	VTTVAsHTSDSDVPSGVTEVVVK	A0A384NKS6	2394.14359
10	VTYTsQEDLVEK	P05156	1491.66145
11	QLGAGsIEECAAK	B2R7F8	1413.60797
12	QVEKEEtNEIQVVNEEPQR	Q8NBJ4	2378.08714
13	SHCIAEVENDEMPADLPsLAADFVESK	A8K9P0	3070.30572
14	SHCIAEVENDGMPADLPsLAADFVESK	B4DPR2	2982.28968
15	SKDHEELSLVAsEAVR	Q96IY4	1849.86915
16	DMPAsEDLQDLQK	P49908	1569.65023
17	DIPTNsPELEETLTHTITK	B4E1C2	2219.0479
18	ATEDEGsEQKIPEATNR	A0A3S8NFS6	1954.83897
19	AEQCCEETAsSISLHGK	A0A024R035	1986.79328

20	AFQYHsKEQQCVIMAENR	B2R7F8	2319.00461
21	ENtVTNDWIPEGEEDDDYLDLEK	P05546	2819.1455
22	VQsTELCAGHLAGGTDSCQGDSGGPLVCFEK	B2R7F8	3317.39087
23	IQMTQSPsSLSASVGDR	A0A5C2FW50	1939.78681
24	sEETKENEGFTVTAEGK	P01024	1935.82192
25	KDsGEDPATCAFQR	Q13103	1661.66253
26	VIQMTQSPSsLSASVGDR	A0A5C2GB04	1958.8889
27	GEVQAMLGQsTEELR	H0Y7L5	1727.76699
28	tSESGELHGLTTEEEFVEGIYK	A0A087WT59	2535.11744
29	YKVVRIEPLGIAPtQASRR	M4XZV0	2314.18324
30	ISAsAEELR	Q13784; P06727	1055.47688
31	THLAPYsDELR	P02647	1381.61477
32	SAGsVESPSVSSTHR	A6XND1	1567.67481
33	EALLDTGADDtIFKDINLPGR	A0A0S2L3P3	2354.12755
34	LDVQPINGsNTSYMLINCNTSVITQACPK	O57038	3318.52043
35	sPEVIPMFSALSEGATPTDLNTMLNTVGGHQAAMQMLK	B5TAH0	4083.89354
36	LLSLGAGEFKsQEHAK	P12259	1794.87859
37	EVQLAVsGGGLVQPGGSLR	A0A5C2GEV4	1903.96372

38	FSVVYAKCDSSPDsAEDVR	P02765	2211.92641
39	NIQMtQSPSSLSASVGDR	A0A5C2GHK5	1973.86341
40	VDNALQSGNSQESVtEQDSK	P0DOX7	2215.93506
41	TNTNVNCPIECFMPLDVQADREDsRE	A0A024R462	3190.32754
42	SIEELARKNLLLEPsLEAK	B3KW95	2313.15027
43	DIQMIQSPsSLSASVGDR	A0A5C2GG67	1970.8889
44	AIQLTQsPSSRSASVGDR	A0A5C2FYB2	1981.93387
45	AIQMTQSPStLSASVGDR	A0A5C2GC00	1970.8889
46	sCESNSPFPVHPGTAECCTK	D6RF35	2344.90324
47	VEtGVGGPQVSGESPVVLGSGTK	A0A6C1AA22	2221.07478
48	MDFSSNGKYLAtCADDR	A0A087WXC6	2046.79328
49	AFyASEIIGDIRQAHCYLSAEK	Q9YU01	2702.17215

Reference

1 L.H. Yi, Y.H. Yan, K.Q. Tang, C.F. Ding, Facile preparation of polymer-grafted ZIF-8-modified magnetic nanospheres for effective identification and capture of phosphorylated and glycosylated peptides, *Anal. Methods*, 2020, **12**, 4657-4664, DOI: 10.1039/d0ay01412e.

2 Y.L. Wu, Q.J. Liu, Y.Q. Xie, C.H. Deng, Core-shell structured magnetic metal-organic framework composites for highly selective enrichment of endogenous N-linked glycopeptides and phosphopeptides, *Talanta*, 2018, **190**, 298-312, DOI: 10.1016/j.talanta.2018.08.010.

3 H. Qi, Z. Li, J.T. Ma, Q. Jia, Tailoring a multifunctional magnetic cationic metal-organic framework composite for synchronous enrichment of phosphopeptides/glycopeptides, *J. Mater. Chem. B,* 2022, **10**, 3560-3566, DOI: 10.1039/d2tb00057a.

4 Y.L. Wu, Q.J. Liu, C.H. Deng, L-cysteine-modified metal-organic frameworks as multifunctional probes for efficient identification of N-linked glycopeptides and phosphopeptides in human crystalline lens, *Anal. Chim. Acta,* 2019, **1061**, 110-121, DOI: 10.1016/j.aca.2019.01.052.

5 Y.T. He, Q. Zheng, H. Huang, Y. Ji, Z. Lin, ynergistic synthesis of hydrophilic hollow zirconium organic frameworks for simultaneous recognition and capture of phosphorylated and glycosylated peptides, *Anal. Chim. Acta,* 2022, **1198,** 339552, DOI: 10.1016/j.aca.2022.339552.