Supporting Information

Dynamic phosphorylation of apoptosis signal regulating kinase 1 (ASK1) in response to oxidative and electrophilic stress

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Table of contents

Figure S1. Annotated MS/MS spectra for each manually validated phosphopeptide.

Figure S2. Graphs of all detected and quantified ASK1 phosphopeptides in the HNE treated cells.

Figure S3. Graphs of all detected and quantified ASK1 phosphopeptides in the H_2O_2 treated cells.

Figure S1. Annotated MS/MS spectra for each manually validated phosphopeptide. Where possible, the phosphorylation was localized to a single residue. When this was not possible with the data at hand, the phosphorylation was localized to the fewest possible sites with sufficient explanatory evidence. Each page lists the peptide sequence, site(s) of modification, MS1 isolation window, precursor mass accuracy, annotated MS/MS spectrum, and a table summarizing the identified peaks for the MS/MS spectrum.

⁷⁹GRGS[79.96633]SVGGGSR⁸⁹



Ser 82/83

Precursor m/z: 528.7345 Precursor mass error: 5.20 ppm



parameter	value
Number of peaks searched	90
Number of fragments searched	756
Number of fragments matched	63
Intensity matched	74 %
Sequence length	11
lon serie matches for "b"	2, 3
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	7, 7, 9, 9, 10
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	4, 5, 6, 7, 8, 9, 10
Ion serie matches for "b -NH3"	2, 3
Ion serie matches for "b -NH3 -H3PO4"	4
Ion serie matches for "y"	1, 2, 3, 4, 5, 6, 7
Ion serie matches for "y -H2O"	4,7
Ion serie matches for "y -H2O -H3PO4"	8, 9
Ion serie matches for "y -H2O -NH3"	2, 3, 5
Ion serie matches for "y -H3PO4"	8, 9
Ion serie matches for "y -NH3"	1, 2, 3, 4, 5
Ion serie matches for "y -NH3 -H3PO4"	10

⁷⁹GRGSS[79.96633]VGGGSRR⁹⁰



Ser 82/83

Precursor m/z: 404.8588 Precursor mass error: -2.06 ppm



parameter	value
Number of peaks searched	186
Number of fragments searched	1485
Number of fragments matched	114
Intensity matched	64 %
Sequence length	12
Ion serie matches for "b"	2, 3, 4
Ion serie matches for "b -H2O"	4
Ion serie matches for "b -H2O -H3PO4"	5, 6, 6, 7, 7, 9, 9
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	5, 6, 7, 9, 11
Ion serie matches for "b -NH3"	2, 3, 8
Ion serie matches for "b -NH3 -H3PO4"	
lon serie matches for "y"	1, 2, 3, 3, 4, 4, 5, 5, 6, 6, 7
Ion serie matches for "y -H2O"	3
Ion serie matches for "y -H2O -H3PO4"	9, 10
Ion serie matches for "y -H2O -NH3"	3, 4, 4, 5, 6, 7
Ion serie matches for "y -H3PO4"	8, 9, 10, 10, 11, 11
Ion serie matches for "y -NH3"	1, 2, 3, 4, 4, 5, 5, 6, 6
Ion serie matches for "y -NH3 -H3PO4"	8, 10, 11

⁸¹GS[79.96633]SVGGGSR⁸⁹



Ser 82/83

Precursor m/z: 422.1718 Precursor mass error: -0.83 ppm



parameter	value
Number of peaks searched	39
Number of fragments searched	356
Number of fragments matched	16
Intensity matched	62 %
Sequence length	9
Ion serie matches for "b"	
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	3
Ion serie matches for "b -H3PO4"	3
Ion serie matches for "y"	1, 3, 4, 5, 6
Ion serie matches for "y -H2O"	3, 7, 7
Ion serie matches for "y -H2O -H3PO4"	
Ion serie matches for "y -H2O -NH3"	5
Ion serie matches for "y -H3PO4"	
Ion serie matches for "y -NH3"	1, 5
Ion serie matches for "y -NH3 -H3PO4"	

⁸¹GS[79.96633]SVGGGSRR⁹⁰



Ser 82/83

Precursor m/z: 500.2227 Precursor mass error: -1.40 ppm



parameter	value
Number of peaks searched	97
Number of fragments searched	502
Number of fragments matched	58
Intensity matched	79 %
Sequence length	10
Ion serie matches for "b"	3
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	3, 8, 9
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	3, 4, 9
Ion serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	
Ion serie matches for "y"	1, 4, 5, 6, 6, 7, 7
Ion serie matches for "y -H2O"	5, 6, 8, 8
Ion serie matches for "y -H2O -H3PO4"	9
Ion serie matches for "y -H2O -NH3"	5, 5, 6, 8, 8
Ion serie matches for "y -H3PO4"	9
Ion serie matches for "y -NH3"	1, 3, 4, 5, 6, 7, 7
Ion serie matches for "y -NH3 -H3PO4"	

¹³⁵LDFGET[79.96633]TVLDR¹⁴⁵



Thr 140/141

Precursor m/z: 673.3052 Precursor mass error: 0.30 ppm



parameter	value
Number of peaks searched	22
Number of fragments searched	684
Number of fragments matched	19
Intensity matched	70 %
Sequence length	11
lon serie matches for "b"	2
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H3PO4"	
Ion serie matches for "y"	1, 2, 3, 4
Ion serie matches for "y -H2O"	5
Ion serie matches for "y -H2O -H3PO4"	6, 8
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	6, 8, 9
Ion serie matches for "y -NH3"	
Ion serie matches for "y -NH3 -H3PO4"	

$^{263} VAQASS [79.96633] SQYFR^{273}$



Ser 268/269

Precursor m/z: 662.2910 Precursor mass error: -1.36 ppm



parameter	value
Number of peaks searched	31
Number of fragments searched	976
Number of fragments matched	27
Intensity matched	86 %
Sequence length	11
Ion serie matches for "b"	2, 3
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	
Ion serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	
Ion serie matches for "y"	1, 2, 3, 4, 7
Ion serie matches for "y -H2O"	5
Ion serie matches for "y -H2O -H3PO4"	6, 6, 7, 8, 9
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	6, 7, 8, 9
Ion serie matches for "y -NH3"	
Ion serie matches for "y -NH3 -H3PO4"	9

³⁵³FHY[79.96633]AFALNR³⁶¹



Tyr 355

Precursor m/z: 609.7716 Precursor mass error: 7.87 ppm



Number of peaks searched Number of fragments searched Number of fragments matched	Turuto
Number of fragments searched Number of fragments matched	27
Number of fragments matched	182
latanaity matched	18
intensity matched	84 %
Sequence length	9
Ion serie matches for "b"	2, 3, 4, 5
Ion serie matches for "b -NH3"	
lon serie matches for "y"	1, 2, 3, 4, 5, 6
Ion serie matches for "y -NH3"	2346

944KKKT[79.96633]QPKLSALSAGSNEYLR963



Thr 947/S952

Precursor m/z: 575.5613 Precursor mass error: -0.52 ppm



parameter	value
Number of peaks searched	108
Number of fragments searched	6332
Number of fragments matched	100
Intensity matched	76 %
Sequence length	20
Ion serie matches for "b"	2, 3, 5, 10, 11, 12, 13
Ion serie matches for "b -H2O"	10, 12
Ion serie matches for "b -H2O -H3PO4"	10, 11, 12, 13, 15
Ion serie matches for "b -H2O -NH3"	12, 16
Ion serie matches for "b -H3PO4"	4, 10, 11, 12, 13, 14
Ion serie matches for "b -NH3"	2
Ion serie matches for "b -NH3 -H3PO4"	4, 10, 12
Ion serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9
Ion serie matches for "y -H2O"	4, 7, 8, 9
Ion serie matches for "y -H2O -H3PO4"	
Ion serie matches for "y -H2O -NH3"	6, 7, 7, 8, 9
Ion serie matches for "y -H3PO4"	
Ion serie matches for "y -NH3"	1, 2, 5, 6, 7, 8, 9
Ion serie matches for "y -NH3 -H3PO4"	

945KKTQPKLS[79.96633]ALSAGSNEYLR963



Thr 947/S952

Precursor m/z: 543.5375 Precursor mass error: -2.85 ppm



parameter	value	
Number of peaks searched	93	
Number of fragments searched	6352	
Number of fragments matched	93	
Intensity matched	89 %	
Sequence length	19	
Ion serie matches for "b"	2, 8, 9, 10, 11	
Ion serie matches for "b -H2O"	3, 4, 7, 9, 10, 11	
Ion serie matches for "b -H2O -H3PO4"	11	
Ion serie matches for "b -H2O -NH3"	4	
Ion serie matches for "b -H3PO4"	9, 10, 11	
Ion serie matches for "b -NH3"	2,3	
Ion serie matches for "b -NH3 -H3PO4"	9, 11	
Ion serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9	
Ion serie matches for "y -H2O"	4, 7, 7	
Ion serie matches for "y -H2O -H3PO4"		
Ion serie matches for "y -H2O -NH3"	6, 7, 7	
Ion serie matches for "y -H3PO4"		
Ion serie matches for "y -NH3"	1, 2, 3, 5, 6, 7, 8, 9	
Ion serie matches for "y -NH3 -H3PO4"	04"	

951LSALS[79.96633]AGSNEYLR963



Ser 955

Precursor m/z: 730.8403 Precursor mass error: 3.28 ppm



parameter	value
Number of peaks searched	28
Number of fragments searched	1250
Number of fragments matched	35
Intensity matched	90 %
Sequence length	13
lon serie matches for "b"	2, 3
Ion serie matches for "b -H2O"	2, 3
Ion serie matches for "b -H2O -H3PO4"	6
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	
Ion serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	
lon serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9
Ion serie matches for "y -H2O"	7
Ion serie matches for "y -H2O -H3PO4"	
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	9, 10, 11, 12
Ion serie matches for "y -NH3"	
Ion serie matches for "y -NH3 -H3PO4"	

951LSALSAGS[79.96633]NEYLR963



Ser 958

Precursor m/z: 730.8427 Precursor mass error: 0 ppm



parameter	value
Number of peaks searched	104
Number of fragments searched	1328
Number of fragments matched	82
Intensity matched	88 %
Sequence length	13
lon serie matches for "b"	2, 3, 4, 6
Ion serie matches for "b -H2O"	2, 3, 4, 5
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	
Ion serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	
lon serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
Ion serie matches for "y -H2O"	4, 9, 11
Ion serie matches for "y -H2O -H3PO4"	7, 8, 9, 9, 10, 12
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	6, 7, 7, 8, 8, 9, 9, 10, 11, 12
Ion serie matches for "y -NH3"	1, 2, 3, 4, 5
Ion serie matches for "y -NH3 -H3PO4"	6, 7, 8, 9

947TQPKLSALSAGS[79.96633]NEYLR963



Ser 955/958

Precursor m/z: 638.9838 Precursor mass error: -2.50 ppm



parameter	value
Number of peaks searched	127
Number of fragments searched	3588
Number of fragments matched	122
Intensity matched	89 %
Sequence length	17
lon serie matches for "b"	2, 5, 6, 7, 8, 9
lon serie matches for "b -H2O"	2, 5, 7, 9
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H2O -NH3"	2,6
Ion serie matches for "b -H3PO4"	
Ion serie matches for "b -NH3"	12
Ion serie matches for "b -NH3 -H3PO4"	
Ion serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9
Ion serie matches for "y -H2O"	4
Ion serie matches for "y -H2O -H3PO4"	7, 9, 11, 12, 12, 15
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	6, 6, 7, 7, 8, 8, 9, 9, 10, 11, 12, 13, 14, 15
Ion serie matches for "y -NH3"	1, 2, 5
Ion serie matches for "y -NH3 -H3PO4"	6, 7, 7, 8, 8, 9, 13, 15

⁹⁴⁶KTQPKLSALSAGS[79.96633]NEYLR⁹⁶³



Ser 955/958

Precursor m/z: 681.6821 Precursor mass error: -2.30 ppm



parameter	value
Number of peaks searched	150
Number of fragments searched	4077
Number of fragments matched	147
Intensity matched	83 %
Sequence length	18
Ion serie matches for "b"	2, 3, 4, 5, 6, 7, 8, 8, 9, 10
Ion serie matches for "b -H2O"	2, 3, 6, 8, 8, 9, 10, 10, 11
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H2O -NH3"	2, 3, 8
Ion serie matches for "b -H3PO4"	
Ion serie matches for "b -NH3"	3, 6, 6
Ion serie matches for "b -NH3 -H3PO4"	
Ion serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15
Ion serie matches for "y -H2O"	4
Ion serie matches for "y -H2O -H3PO4"	9, 10, 11, 12, 12, 15, 16
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	6, 6, 7, 7, 8, 8, 9, 9, 10, 11, 12, 13, 15, 17
Ion serie matches for "y -NH3"	1, 2
Ion serie matches for "y -NH3 -H3PO4"	6, 7, 7, 8, 8, 9, 9, 16

951LSALSAGS[79.96633]NEYLR963



Ser 955/958

Precursor m/z: 730.8452 Precursor mass error: -3.42 ppm



parameter	value
Number of peaks searched	78
Number of fragments searched	1328
Number of fragments matched	66
Intensity matched	89 %
Sequence length	13
Ion serie matches for "b"	2, 3, 4, 6
Ion serie matches for "b -H2O"	2, 3, 5
lon serie matches for "b -H2O -H3PO4"	
lon serie matches for "b -H2O -NH3"	
lon serie matches for "b -H3PO4"	
lon serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	
lon serie matches for "y"	1, 2, 3, 4, 5, 6, 7, 8, 9, 9, 10, 11
lon serie matches for "y -H2O"	4, 9
lon serie matches for "y -H2O -H3PO4"	7, 8, 9, 9, 10, 11, 12
lon serie matches for "y -H2O -NH3"	
lon serie matches for "y -H3PO4"	6, 7, 7, 8, 8, 9, 9, 10, 11, 12
lon serie matches for "y -NH3"	4
Ion serie matches for "y -NH3 -H3PO4"	7, 8, 9

¹⁰⁰⁰TRAKS[79.96633]C[57.02146]GERDVK¹⁰¹¹



Thr 1000/S1004

Precursor m/z: 496.2332 Precursor mass error: -1.21 ppm



parameter	value
Number of peaks searched	170
Number of fragments searched	1845
Number of fragments matched	84
Intensity matched	62 %
Sequence length	12
Ion serie matches for "b"	2, 3, 4, 10, 10
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	5, 5, 6, 8, 10
Ion serie matches for "b -H2O -NH3"	2
Ion serie matches for "b -H3PO4"	5, 5, 6, 7, 8, 8, 9, 10, 10, 11
Ion serie matches for "b -NH3"	2,3
Ion serie matches for "b -NH3 -H3PO4"	9, 10, 10
Ion serie matches for "y"	2, 3, 4, 4, 5, 6, 6, 7, 7
Ion serie matches for "y -H2O"	5, 6, 7
Ion serie matches for "y -H2O -H3PO4"	8, 9, 10
Ion serie matches for "y -H2O -NH3"	6
Ion serie matches for "y -H3PO4"	8, 8, 10
Ion serie matches for "y -NH3"	2, 6, 7
Ion serie matches for "y -NH3 -H3PO4"	8,8

¹⁰⁰⁰TRAKS[79.96633]C[57.02146]GERDVKGIR¹⁰¹⁴



Thr 1000/S1004

Precursor m/z: 453.9788 Precursor mass error: -1.93 ppm



parameter	value
Number of peaks searched	168
Number of fragments searched	3824
Number of fragments matched	103
Intensity matched	77 %
Sequence length	15
Ion serie matches for "b"	2, 3, 4, 4, 9, 13
Ion serie matches for "b -H2O"	4, 9
Ion serie matches for "b -H2O -H3PO4"	5, 5, 10
Ion serie matches for "b -H2O -NH3"	2
Ion serie matches for "b -H3PO4"	5, 5, 8, 9, 10, 10, 11, 12, 13, 14
Ion serie matches for "b -NH3"	2, 3, 4
Ion serie matches for "b -NH3 -H3PO4"	9, 10, 11
Ion serie matches for "y"	1, 2, 3, 4, 4, 5, 5, 6, 7, 8, 9, 10
Ion serie matches for "y -H2O"	7, 10, 10
Ion serie matches for "y -H2O -H3PO4"	
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	11, 11, 13
Ion serie matches for "y -NH3"	1, 2, 3, 4, 4, 5, 7, 9, 10, 10
Ion serie matches for "y -NH3 -H3PO4"	11, 11, 12, 14

¹⁰⁰²AKS[79.96633]C[57.02146]GERDVK¹⁰¹¹



Ser 1004

Precursor m/z: 615.2717 Precursor mass error: -1.38 ppm



parameter	value
Number of peaks searched	106
Number of fragments searched	758
Number of fragments matched	60
Intensity matched	78 %
Sequence length	10
Ion serie matches for "b"	2, 8, 8
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	3, 8
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	3, 7, 8, 8, 9, 9
Ion serie matches for "b -NH3"	2
Ion serie matches for "b -NH3 -H3PO4"	3, 8
Ion serie matches for "y"	2, 3, 4, 5, 6, 7, 8
Ion serie matches for "y -H2O"	4, 5, 6, 7
Ion serie matches for "y -H2O -H3PO4"	8, 8, 9
Ion serie matches for "y -H2O -NH3"	
Ion serie matches for "y -H3PO4"	8, 8, 9
Ion serie matches for "y -NH3"	2,7
Ion serie matches for "y -NH3 -H3PO4"	8, 8, 9

¹⁰⁵⁷ILT[79.96633]EDQDKIVR¹⁰⁶⁷



Thr 1059

Precursor m/z: 470.5735 Precursor mass error: -1.70 ppm



parameter	value
Number of peaks searched	81
Number of fragments searched	1326
Number of fragments matched	51
Intensity matched	69 %
Sequence length	11
lon serie matches for "b"	2
lon serie matches for "b -H2O"	
lon serie matches for "b -H2O -H3PO4"	
lon serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	
lon serie matches for "b -NH3"	
lon serie matches for "b -NH3 -H3PO4"	
lon serie matches for "y"	1, 2, 3, 4, 5, 6, 6, 7, 7, 8, 8
lon serie matches for "y -H2O"	6, 8, 8
lon serie matches for "y -H2O -H3PO4"	9
lon serie matches for "y -H2O -NH3"	
lon serie matches for "y -H3PO4"	9, 9, 10
lon serie matches for "y -NH3"	2, 4, 5, 6, 6, 7, 7
Ion serie matches for "y -NH3 -H3PO4"	9, 10

¹²⁴⁰S[79.96633]LNVQLGR¹²⁴⁷



Ser 1240

Precursor m/z: 483.7427 Precursor mass error: -1.34 ppm



parameter	value
Number of peaks searched	55
Number of fragments searched	262
Number of fragments matched	37
Intensity matched	77 %
Sequence length	8
Ion serie matches for "b"	2, 3
Ion serie matches for "b -H2O"	
Ion serie matches for "b -H2O -H3PO4"	
Ion serie matches for "b -H2O -NH3"	
Ion serie matches for "b -H3PO4"	2, 3, 4, 5
Ion serie matches for "b -NH3"	
Ion serie matches for "b -NH3 -H3PO4"	3
lon serie matches for "y"	1, 2, 3, 4, 5, 6, 7
Ion serie matches for "y -NH3"	1, 2, 3, 4, 6

Figure S2. Graphs of all detected and quantified ASK1 phosphopeptides in the HNE treated cells. For each concentration point (10 and 50 μ M) the peptide peak are was compared against the peptide peak area for the control sample (0 μ M). Graphs are shown for (A) Ser 83 (B) Thr 947|Ser 952 (C) Ser 955|Ser 958 (D) Thr 1000|Ser 1004 (E) Thr 1059 (F) Ser 1240.



Figure S2.



T947|S952 KKKTQPKLSALSAGSNEYLR





Normalized peak area



T947|S952 KKK**T**QPKL**S**ALSAGSNEYLR



С

S955|S958 KTQPKLSAL**S**AG**S**NEYLR



S955|S958 KTQPKLSAL**S**AG**S**NEYLR



Figure S2.



С



S958











D





Figure S2.





µM HNE

Figure S2.

µM HNE



ns

ŝ

F

Figure S3. Graphs of all detected and quantified ASK1 phosphopeptides in the H_2O_2 treated cells. For each concentration point (500 and 5000 μ M) the peptide peak are was compared against the peptide peak area for the control sample (0 μ M). Graphs are shown for (A) Ser 83 (B) The 140|Thr 141 (C) Ser 268|Ser 269 (D) Tyr 355 (E) Thr 947|Ser 952 (F) Ser 955 (G) Ser 958 (H) Ser 1004 (I) Ser 1240.



Figure S3.



Figure S3.

Y355 FHY[+80]AFALNR







F

D

T947|S952 KKK**T**QPKL**S**ALSAGSNEYLR









 $\mu M H_2O_2$

0

5000



ns 8.0×10⁶ 6.0×106 4.0×106 2.0×106

Normalized peak area

0

T947|S952 KKK**T**QPKL**S**ALSAGSNEYLR



Y355 FHY[+80]AFALNR



Figure S3.

G