

Supplementary material

Supplementary Table 1.

Protein information (Name, Short name, UniprotID and coding gene) for the 80 proteins used.

Supplementary Table 2.

Results from the 28 proteins that were significant in the Discovery cohort in the univariate analysis. P-values and mean differences in normalized values between cases and controls in both the discovery and replication cohorts.

Supplementary Table 3.

Results (Beta, variance explained and p-value) from modelling normalized abundance levels from time to diagnosis, before and after diagnosis, for the 80 proteins.

Supplementary Table 4.

Results (P-values and mean differences) from comparing normalized protein abundance levels in the replication cohort between control samples and samples taken before and after diagnosis for the 28 proteins that were significantly changed in the univariate analysis in the discovery cohort.

Supplementary Table 1

Protein Name	UniprotID	Gene	Short name
Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)	Q13541	EIF4EBP1	4E-BP1
Adenosine Deaminase (ADA)	P00813	ADA	ADA
Agouti-related protein (AGRP)	O00253	AGRP	AGRP
Amphiregulin (AR)	P15514	AREG	AR
Axin-1 (AXIN1)	O15169	AXIN1	AXIN1
Brain-derived neurotrophic factor	P23560	BDNF	BDNF
Beta-nerve growth factor (Beta-NGF)	P01138	NGF	Beta-NGF
C-C motif chemokine 19 (CCL19)	Q99731	CCL19	CCL19
C-C motif chemokine 20 (CCL20)	P78556	CCL20	CCL20
C-C motif chemokine 23 (CCL23)	P55773	CCL23	CCL23
C-C motif chemokine 28 (CCL28)	Q9NRJ3	CCL28	CCL28
C-C motif chemokine 3 (CCL3)	P10147	CCL3	CCL3
C-C motif chemokine 4 (CCL4)	P13236	CCL4	CCL4
Natural killer cell receptor 2B4 (CD244)	Q9BZW8	CD244	CD244
CD40L receptor (CD40)	P25942	CD40	CD40
CD40 ligand (CD40-L)	P29965	CD40LG	CD40-L
T-cell surface glycoprotein CD5 (CD5)	P06127	CD5	CD5
CUB domain-containing protein 1 (CDCP1)	Q9H5V8	CDCP1	CDCP1
Macrophage colony-stimulating factor 1 (CSF-1)	P09603	CSF1	CSF1
Cystatin D (CST5)	P28325	CST5	CST5
Fractalkine (CX3CL1)	P78423	CX3CL1	CX3CL1
C-X-C motif chemokine 1 (CXCL1)	P09341	CXCL1	CXCL1
C-X-C motif chemokine 10 (CXCL10)	P02778	CXCL10	CXCL10
C-X-C motif chemokine 5 (CXCL5)	P42830	CXCL5	CXCL5
C-X-C motif chemokine 9 (CXCL9)	Q07325	CXCL9	CXCL9
Dickkopf-related protein 1 (Dkk-1)	O94907	DKK1	Dkk-1
Fas antigen ligand (FasL)	P48023	FASLG	FASLG
Fibroblast growth factor 21 (FGF-21)	Q9NSA1	FGF21	FGF-21
Fibroblast growth factor 23 (FGF-23)	Q9GZV9	FGF23	FGF-23
Fibroblast growth factor 5 (FGF-5)	Q8NF90	FGF5	FGF-5
Folate receptor alpha (FR-alpha)	P15328	FOLR1	FRalpha
Follistatin (FS)	P19883	FST	FS
Proheparin-binding EGF-like growth factor (HB-EGF)	Q99075	HBEGF	HB-EGF
Glial cell line-derived neurotrophic factor (GDNF)	P39905	GDNF	hGDNF
Hepatocyte growth factor (HGF)	P14210	HGF	HGF
Heat shock 27 kDa protein (HSP 27)	P04792	HSPB1	HSP-27
Interleukin-10 (IL-10)	P22301	IL10	IL-10
Interleukin-10 receptor subunit alpha (IL-10RA)	Q13651	IL10RA	IL-10RA
Interleukin-12 subunit beta (IL-12B)	P29460	IL12B	IL-12B
Interleukin-15 receptor subunit alpha (IL-15RA)	Q13261	IL15RA	IL-15RA
Interleukin-17A (IL-17A)	Q16552	IL17A	IL-17A
Interleukin-17C (IL-17C)	Q9POM4	IL17C	IL-17C
Interleukin-18 (IL-18)	Q14116	IL18	IL-18
Interleukin-18 receptor 1 (IL-18R1)	Q13478	IL18R1	IL-18R1
Interleukin-20 receptor subunit alpha (IL-20RA)	Q9UHF4	IL20RA	IL-20RA
Interleukin-5 (IL-5)	P05113	IL5	IL-5
Interleukin-6 (IL-6)	P05231	IL6	IL-6
Interleukin-7 (IL-7)	P13232	IL7	IL-7
Interleukin-8 (IL-8)	P10145	CXCL8	IL-8
Interleukin-27 (IL-27)	Q8NEV9, Q14213	IL27, EBI3	IL-27
Melusin (ITGB1BP2)	Q9UKP3	ITGB1BP2	ITGB1BP2
Leukemia inhibitory factor receptor (LIF-R)	P42702	LIFR	LIF-R
MHC class I polypeptide-related sequence A/B (MIC-A/B)	Q29983, Q29980	MICA, MICB	MIC-A
Midkine (MK)	P21741	MDK	MK
Matrix metalloproteinase-1 (MMP-1)	P03956	MMP1	MMP-1
Matrix metalloproteinase-10 (MMP-10)	P09238	MMP10	MMP-10
Mucin-16 (MUC-16)	Q8WXI7	MUC16	MUC16
NF-kappa-B essential modulator (NEMO)	Q9Y6K9	IKBKG	NEMO
Neurotrophin-3 (NT-3)	P20783	NTF3	NT-3
Osteoprotegerin (OPG)	O00300	TNFRSF11B	OPG
Oncostatin-M (OSM)	P13725	OSM	OSM
Pappalysin-1 (PAPPA)	Q13219	PAPPA	PAPP-A
Platelet-derived growth factor subunit B (PDGF subunit B)	P01127	PDGFB	PDGF-subunit-B

P-selectin glycoprotein ligand 1 (PSGL-1)	Q14242	SELPLG	PSGL-1
Pentraxin-related protein PTX3 (PTX3)	P26022	PTX3	PTX3
Receptor for advanced glycosylation end products (RAGE)	Q15109	AGER	RAGE
Stem cell factor (SCF)	P21583	KITLG	SCF
SIR2-like protein 2 (SIRT2)	Q8IXJ6	SIRT2	SIRT2
Signaling lymphocytic activation molecule (SLAMF1)	Q13291	SLAMF1	SLAMF1
Proto-oncogene tyrosine-protein kinase Src (SRC)	P12931	SRC	SRC
Sulfotransferase 1A1 (ST1A1)	P50225	SULT1A1	ST1A1
STAM-binding protein (STAMPB)	O95630	STAMPB	STAMPB
Transforming growth factor alpha (TGF-alpha)	P01135	TGFA	TGFA
TNF-beta (TNFB)	P01374	LTA	TNFB
Tumor necrosis factor receptor superfamily member 9 (TNFRSF9)	Q07011	TNFRSF9	TNFRSF9
Tumor necrosis factor ligand superfamily member 14 (TNFSF14)	O43557	TNFSF14	TNFSF14
TNF-related apoptosis-inducing ligand (TRAIL)	P50591	TNFSF10	TRAIL
TNF-related activation-induced cytokine (TRANCE)	O14788	TNFSF11	TRANCE
Tumor necrosis factor (Ligand) superfamily, member 12 (TWEAK)	O43508	TNFSF12	TWEAK
Vascular endothelial growth factor A (VEGF-A)	P15692	VEGFA	VEGF-A

Supplementary Table 2

Protein Short Name	Discovery Cohort		Replication Cohort	
	P-value	mean Difference (case-ctrl)	P-value	mean Difference (case-ctrl)
ITGB1BP2	1,36E-41	6,87	3,93E-06	0,86
PTX3	6,67E-40	4,25	5,97E-17	1,86
SIRT2	4,19E-39	5,26	8,00E-03	0,40
AXIN1	6,23E-39	5,56	1,93E-01	-0,19
4E-BP1	3,14E-37	3,68	2,98E-02	0,34
STAMBP	4,36E-35	5,22	9,30E-01	-0,01
FS	1,38E-28	2,74	1,00E-04	0,73
HB-EGF	9,35E-28	6,03	2,85E-06	1,17
SRC	1,22E-27	2,67	1,41E-03	0,67
NEMO	2,47E-27	4,61	2,84E-04	0,61
hGDNF	1,06E-18	2,79	7,52E-02	0,30
MK	1,74E-16	1,86	9,91E-11	1,44
PAPP-A	3,13E-16	1,09	5,19E-07	1,13
IL-27	3,92E-16	1,71	2,28E-14	1,63
CD40-L	3,32E-13	1,86	5,59E-07	0,92
NT-3	1,35E-10	1,42	6,74E-01	0,07
VEGF-A	3,15E-10	1,78	9,22E-02	0,41
IL-7	4,44E-10	1,39	3,94E-01	0,13
RAGE	4,89E-09	1,12	1,26E-02	-0,45
IL-15RA	1,02E-06	0,89	6,27E-01	0,08
CD40	1,24E-06	1,14	3,08E-01	-0,16
AR	1,10E-05	1,08	1,35E-11	1,09
HSP-27	2,24E-05	0,70	3,84E-07	0,96
ST1A1	2,61E-05	0,84	6,82E-01	0,06
IL-5	4,56E-05	0,89	3,78E-01	-0,09
CCL28	7,47E-05	0,75	9,37E-03	0,40
CD244	1,43E-04	0,78	3,71E-05	-0,59
FR-alpha	2,16E-04	0,67	2,09E-03	0,66

Supplementary Table 3

Protein Short Name	Before Diagnosis			After Diagnosis		
	Beta	Variance Explained	p-value	Beta	Variance Explained	p-value
4E-BP1	-6,40E-05	5,35E-03	2,79E-01	1,08E-05	2,10E-04	8,36E-01
ADA	-3,05E-05	1,80E-03	5,31E-01	-9,07E-06	3,25E-04	7,96E-01
AGRP	1,15E-04	1,86E-02	4,27E-02	-3,75E-05	2,41E-03	4,82E-01
AR	-1,01E-04	1,79E-02	4,70E-02	6,89E-05	1,95E-02	4,40E-02
AXIN1	-1,06E-05	1,53E-04	8,55E-01	-1,17E-04	2,06E-02	3,87E-02
BDNF	-4,20E-06	2,47E-05	9,41E-01	-6,49E-05	6,71E-03	2,39E-01
Beta-NGF	-6,01E-05	5,98E-03	2,52E-01	-2,36E-05	1,15E-03	6,27E-01
CCL19	7,91E-05	7,70E-03	1,94E-01	5,72E-05	7,45E-03	2,15E-01
CCL20	-6,26E-05	6,75E-03	2,24E-01	7,72E-06	1,17E-04	8,77E-01
CCL23	8,52E-05	9,48E-03	1,49E-01	8,24E-05	1,41E-02	8,73E-02
CCL28	-2,04E-05	7,41E-04	6,87E-01	7,27E-05	7,77E-03	2,05E-01
CCL3	-1,45E-04	2,96E-02	1,03E-02	-7,07E-05	8,81E-03	1,77E-01
CCL4	-1,69E-04	6,27E-02	1,69E-04	-7,74E-06	2,12E-04	8,35E-01
CD244	1,91E-05	5,09E-04	7,39E-01	5,07E-06	6,37E-05	9,09E-01
CD40	-8,55E-05	1,12E-02	1,17E-01	-7,82E-05	1,50E-02	7,78E-02
CD40-L	-7,14E-05	6,44E-03	2,35E-01	-5,99E-05	5,32E-03	2,95E-01
CD5	-1,05E-04	1,74E-02	5,00E-02	2,67E-05	1,79E-03	5,45E-01
CDCP1	-4,17E-05	2,38E-03	4,71E-01	-4,12E-05	3,41E-03	4,02E-01
CSF-1	-4,26E-05	1,79E-03	5,32E-01	3,74E-05	2,23E-03	4,98E-01
CST5	-7,89E-06	8,76E-05	8,90E-01	6,17E-06	9,88E-05	8,87E-01
CX3CL1	-1,00E-04	1,73E-02	5,10E-02	3,31E-05	2,20E-03	5,01E-01
CXCL1	-1,35E-04	2,08E-02	3,22E-02	-9,69E-05	1,62E-02	6,73E-02
CXCL10	-8,28E-05	9,70E-03	1,44E-01	9,12E-05	1,08E-02	1,35E-01
CXCL5	-3,35E-06	1,39E-05	9,56E-01	-4,37E-05	3,45E-03	3,99E-01
CXCL9	1,62E-07	3,76E-08	9,98E-01	1,28E-04	3,32E-02	8,45E-03
Dkk-1	-3,93E-05	1,97E-03	5,11E-01	-2,96E-05	1,47E-03	5,82E-01
FASLG	1,18E-05	1,40E-04	8,61E-01	1,45E-05	2,38E-04	8,25E-01
FGF-21	-9,16E-05	1,35E-02	8,48E-02	9,12E-05	1,70E-02	6,07E-02
FGF-23	-3,32E-05	1,86E-03	5,24E-01	6,72E-05	2,72E-02	1,73E-02
FGF-5	-6,23E-05	5,63E-03	2,67E-01	8,15E-05	1,09E-02	1,34E-01
FR-alpha	-1,87E-04	5,81E-02	2,99E-04	-2,72E-05	1,79E-03	5,44E-01
FS	2,18E-05	5,77E-04	7,23E-01	1,95E-05	7,24E-04	7,00E-01
HB-EGF	-1,79E-04	2,62E-02	1,61E-02	-5,42E-05	4,32E-03	3,45E-01
hGDNF	3,75E-05	2,05E-03	5,03E-01	4,40E-05	3,34E-03	4,07E-01
HGF	-5,37E-05	4,35E-03	3,29E-01	8,68E-05	1,32E-02	9,80E-02
HSP-27	-2,82E-05	1,47E-03	5,71E-01	-2,87E-05	1,81E-03	5,42E-01
IL-10	-8,54E-05	1,17E-02	1,09E-01	5,50E-05	3,99E-03	3,65E-01
IL-10RA	-3,42E-05	3,22E-03	4,01E-01	1,43E-05	7,66E-04	6,92E-01
IL-12B	-1,02E-04	1,43E-02	7,63E-02	-6,47E-05	7,21E-03	2,23E-01
IL-15RA	8,63E-07	1,20E-06	9,87E-01	2,18E-05	7,84E-04	6,88E-01
IL-17A	-6,23E-05	6,81E-03	2,22E-01	2,41E-05	1,09E-03	6,36E-01
IL-17C	-8,44E-05	1,17E-02	1,09E-01	7,97E-05	1,55E-02	7,32E-02
IL-18	2,70E-05	1,18E-03	6,12E-01	-2,44E-05	1,56E-03	5,72E-01
IL-18R1	2,60E-05	1,07E-03	6,29E-01	-2,68E-06	1,77E-05	9,52E-01
IL-20RA	-6,63E-05	2,34E-02	2,29E-02	5,72E-05	1,39E-02	8,99E-02
IL-27	6,70E-05	6,54E-03	2,31E-01	1,17E-04	2,55E-02	2,12E-02
IL-5	-1,31E-05	6,46E-04	7,07E-01	-1,58E-05	8,57E-04	6,75E-01
IL-6	-5,11E-05	4,87E-03	3,02E-01	-3,74E-05	1,81E-03	5,42E-01
IL-7	-9,23E-05	1,29E-02	9,15E-02	-4,98E-05	5,16E-03	3,02E-01
IL-8	-6,45E-05	6,82E-03	2,21E-01	3,59E-05	3,48E-03	3,97E-01
ITGB1BP2	-1,09E-06	1,76E-06	9,84E-01	-1,13E-04	2,33E-02	2,78E-02
LIF-R	-2,97E-05	1,13E-03	6,19E-01	7,69E-05	9,42E-03	1,63E-01
MIC-A	-1,31E-04	1,47E-02	7,18E-02	4,77E-05	2,77E-03	4,50E-01
MK	-9,33E-05	1,35E-02	8,54E-02	1,72E-05	6,92E-04	7,06E-01
MMP-1	-1,58E-04	3,48E-02	5,39E-03	-1,93E-05	6,48E-04	7,15E-01
MMP-10	-1,52E-04	4,29E-02	1,96E-03	-1,35E-05	6,27E-04	7,20E-01
MUC-16	-5,67E-05	5,18E-03	2,87E-01	4,05E-05	4,04E-03	3,62E-01
NEMO	-1,55E-05	3,22E-04	7,91E-01	-8,66E-05	1,07E-02	1,37E-01
NT-3	2,81E-07	1,04E-07	9,96E-01	2,68E-05	1,43E-03	5,88E-01
OPG	-4,52E-05	3,29E-03	3,96E-01	8,74E-06	2,14E-04	8,34E-01

OSM	-2,91E-05	1,45E-03	5,74E-01	1,51E-04	4,88E-02	1,35E-03
PAPP-A	-4,21E-05	2,55E-03	4,55E-01	1,32E-05	3,56E-04	7,87E-01
PDGF-subunit-B	-1,09E-04	1,55E-02	6,47E-02	-9,43E-05	1,64E-02	6,50E-02
PSGL-1	1,22E-04	1,53E-02	6,60E-02	2,37E-04	3,85E-02	4,50E-03
PTX3	-3,66E-05	2,01E-03	5,07E-01	1,12E-04	2,10E-02	3,69E-02
RAGE	-6,84E-05	6,19E-03	2,44E-01	4,53E-05	3,01E-03	4,32E-01
SCF	-1,73E-04	2,68E-02	1,48E-02	2,78E-05	1,26E-03	6,10E-01
SIRT2	-4,45E-05	2,82E-03	4,32E-01	-1,04E-04	2,09E-02	3,70E-02
SLAMF1	1,61E-05	4,15E-04	7,63E-01	-6,26E-05	4,46E-03	3,38E-01
SRC	-5,87E-05	2,52E-03	4,58E-01	6,91E-05	3,64E-03	3,87E-01
ST1A1	9,87E-06	1,49E-04	8,57E-01	-1,34E-04	3,17E-02	1,01E-02
STAMBP	-4,94E-05	3,49E-03	3,82E-01	-7,75E-05	1,07E-02	1,37E-01
TGFA	4,41E-07	1,86E-07	9,95E-01	1,13E-04	1,44E-02	8,37E-02
TNFB	-1,38E-04	2,87E-02	1,16E-02	3,64E-05	4,05E-03	3,61E-01
TNFRSF9	-1,62E-04	2,54E-02	1,76E-02	5,41E-05	4,91E-03	3,14E-01
TNFSF14	-6,82E-06	8,18E-05	8,94E-01	-1,85E-05	8,02E-04	6,85E-01
TRAIL	-5,89E-05	6,27E-03	2,41E-01	7,54E-05	1,47E-02	8,06E-02
TRANCE	-1,59E-06	3,78E-06	9,77E-01	-1,60E-05	6,71E-04	7,10E-01
TWEAK	-1,18E-04	1,36E-02	8,41E-02	-4,97E-05	2,97E-03	4,35E-01
VEGF-A	-7,45E-05	7,19E-03	2,09E-01	-1,43E-05	3,37E-04	7,92E-01

Supplementary Table 4

Protein Short Name	Mean abundance levels (Normalized)			P-values (two-sided, wilcoxon-test)			
	Before Diagnosis	Controls (1328 to 6166 days prior to diagnosis)	After Diagnosis (28 to 1605 days)	At diagnosis	Before vs Control	Control vs After	Before vs After
4E-BP1	-2,12E-01	-5,78E-02	-1,46E-01	2,58E-01	3,41E-01	5,79E-01	6,94E-01
AR	-2,25E-01	-6,40E-02	-1,56E-01	1,07E+00	2,49E-01	4,58E-01	5,92E-01
AXIN1	-4,87E-02	-1,59E-02	5,37E-02	-2,59E-01	8,37E-01	6,68E-01	5,57E-01
CCL28	-1,47E-01	-1,11E-01	1,90E-01	3,10E-01	8,00E-01	7,51E-02	4,21E-02
CD244	3,22E-02	7,83E-04	1,67E-01	-6,70E-01	8,42E-01	2,32E-01	3,70E-01
CD40	-1,31E-01	9,09E-03	3,90E-02	-2,13E-01	3,50E-01	8,29E-01	2,43E-01
CD40-L	-1,59E-01	3,03E-03	2,99E-03	8,94E-01	3,24E-01	1,00E+00	3,73E-01
FR-alpha	-4,02E-01	5,90E-04	-2,40E-01	6,35E-01	4,87E-03	9,99E-02	2,59E-01
FS	-1,33E-02	-1,12E-01	1,44E-01	6,95E-01	5,56E-01	8,53E-02	3,57E-01
HB-EGF	-3,56E-01	-7,25E-02	-1,20E-01	1,11E+00	1,66E-01	7,80E-01	2,66E-01
hGDNF	-9,94E-02	-1,61E-01	6,76E-02	1,31E-01	6,88E-01	1,61E-01	3,18E-01
HSP-27	-4,10E-01	-4,40E-01	-4,05E-01	4,89E-01	8,28E-01	8,17E-01	9,75E-01
IL-15RA	-1,25E-01	-3,90E-02	-4,29E-02	-2,22E-02	5,55E-01	9,81E-01	6,25E-01
IL-27	1,50E-02	-4,51E-02	-1,79E-02	1,55E+00	6,95E-01	8,56E-01	8,36E-01
IL-5	-9,09E-01	-8,86E-01	-9,80E-01	-9,44E-01	8,06E-01	2,87E-01	4,01E-01
IL-7	-1,65E-01	-1,31E-02	5,57E-02	6,21E-02	3,10E-01	6,35E-01	1,43E-01
ITGB1BP2	-2,52E-01	-2,92E-01	-2,62E-01	5,18E-01	7,92E-01	8,49E-01	9,49E-01
MK	-2,07E-01	-1,76E-02	-1,13E-02	1,41E+00	2,02E-01	9,65E-01	1,98E-01
NEMO	-4,47E-02	-3,07E-02	7,48E-02	5,79E-01	9,31E-01	5,24E-01	5,13E-01
NT-3	-1,14E-01	-2,81E-02	1,13E-01	-1,36E-02	5,95E-01	3,71E-01	1,71E-01
PAPP-A	-1,01E-01	-8,89E-02	-1,90E-01	1,00E+00	9,36E-01	5,21E-01	5,91E-01
PTX3	-1,30E-01	-8,87E-03	-2,51E-01	1,78E+00	4,23E-01	1,19E-01	4,62E-01
RAGE	-2,36E-01	-6,10E-03	-3,07E-01	-5,76E-01	1,53E-01	8,72E-02	6,98E-01
SIRT2	-1,26E-01	-2,61E-02	1,56E-02	3,34E-01	5,19E-01	7,87E-01	3,82E-01
SRC	-3,53E-01	-9,59E-02	-3,55E-01	4,86E-01	2,36E-01	2,36E-01	9,91E-01
ST1A1	-4,45E-02	-2,01E-02	3,43E-02	-1,31E-02	8,71E-01	7,25E-01	6,21E-01
STAMBP	-1,39E-01	-1,44E-02	-1,56E-02	-8,02E-02	4,21E-01	9,94E-01	4,53E-01
VEGF-A	-1,89E-01	1,63E-02	2,52E-02	3,36E-01	2,06E-01	9,54E-01	2,14E-01