

Supplementary Information File 1

Identification of upstream immune regulators that target protein co-expression networks significantly associated with early-stage micropapillary/solid predominant lung adenocarcinomas

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Table S1. Relationship between module eigen-proteins and the clinical traits of three subtypes LPA, MPA, and SPA.

Each row in the embedded table represents weighted gene co-expression network analysis results for each module. The first and second columns in the table represent the module identification and color name of the module, respectively. The third column represents the number of proteins in each module. The table is color-coded by the correlation coefficient according to the color legend on the right side of the seventh column, in which the intensity and direction of the correlations are indicated (red, positive correlation; blue, negative correlation). The eighth to tenth columns present the *p*-values of the correlation coefficients, and the eleventh to fourteenth columns are *q*-values by multiple testing correction using the Benjamini–Hochberg method, where significant *p*- and *q*-values (< 0.05) are highlighted in bright red background.

The fifteenth to eighteenth columns present results of the statistical over-representative analysis (ORA) using the hypergeometric overlapping test of all the WGCNA modules with proteins upregulated (more than twice) uniquely for the individual subtypes: LPA, MPA, and SPA, where the Benjamini–Hochberg corrected significant *q*-values (< 0.05) are highlighted in bright red background.

Module ID.	Module color	Number of module proteins	Corrlation (Cor.)			p-value			BH-corrected q-value				Hypergeometric overlapping BH-corrected q-value			
			LPA	MPA	SPA	LPA	MPA	SPA	LPA	MPA	SPA	Max q-value	LPA	MPA	SPA	Max q-value
WM23	darkgrey	29	-0.150	0.910	-0.660	0.651	3.38E-05	0.0189	0.7660	0.0014	0.1080	0.0014	1.0000	1.661E-17	1.0000	1.661E-17
WM20	tan	57	0.460	0.530	-0.910	0.128	0.0784	4.73E-05	0.6400	0.6270	0.0019	0.0019	1.0000	0.0418	0.0052	5.190E-03
WM25	cyan	58	0.870	-0.110	-0.730	0.000254	0.729	0.00688	0.0100	0.7880	0.0917	0.0102	6.976E-07	1.0000	1.939E-04	6.976E-07
WM1	pink	91	-0.700	-0.180	0.820	0.012	0.583	0.00108	0.1200	0.8040	0.0216	0.0216	6.867E-03	1.0000	0.0035	3.484E-03
WM33	greenyellow	67	0.810	-0.290	-0.520	0.00143	0.357	0.0851	0.0290	0.9520	0.2840	0.0286	4.943E-18	1.0000	1.0000	4.943E-18
WM24	darkorange	23	-0.220	0.790	-0.480	0.5	0.00239	0.111	0.8330	0.0478	0.3420	0.0478	1.0000	3.166E-14	1.0000	3.166E-14
WM8	darkmagenta	11	0.760	-0.016	-0.710	0.00445	0.96	0.00988	0.0590	0.9600	0.0790	0.0593	1.590E-02	1.0000	1.0000	1.590E-02
WM17	lightgreen	41	0.420	0.360	-0.730	0.17	0.244	0.00759	0.6800	0.8130	0.0759	0.0759	4.720E-02	0.0617	0.0045	4.548E-03
WM19	lightcyan	48	0.610	0.130	-0.700	0.034	0.698	0.0119	0.2720	0.8460	0.0793	0.0793	7.165E-02	9.933E-02	1.0000	7.165E-02
WM11	darkred	35	-0.170	0.720	-0.470	0.6	0.00792	0.12	0.8000	0.1060	0.3430	0.1056	4.349E-03	3.895E-14	1.0000	3.895E-14
WM9	saddlebrown	20	0.330	0.330	-0.610	0.291	0.297	0.0365	0.5820	0.9140	0.1830	0.1825	1.713E-02	1.0000	1.0000	1.713E-02
WM2	turquoise	516	-0.340	-0.280	0.570	0.275	0.379	0.0512	0.6110	0.8920	0.2280	0.2276	8.521E-43	1.0000	2.885E-126	2.885E-126
WM32	violet	19	0.610	-0.370	-0.260	0.035	0.233	0.421	0.2330	0.8470	0.6480	0.2333	1.895E-12	1.0000	1.0000	1.895E-12
WM10	plum1	12	0.380	0.200	-0.540	0.227	0.525	0.0703	0.7570	0.8080	0.2560	0.2556	2.373E-01	1.0000	1.0000	2.373E-01
WM38	skyblue	21	0.460	0.120	-0.540	0.135	0.708	0.0674	0.6000	0.8330	0.2700	0.2696	9.674E-01	1.0000	1.0000	9.674E-01
WM35	sienna3	15	0.390	0.120	-0.470	0.216	0.721	0.123	0.7850	0.8010	0.3280	0.328	1.005E+00	1.0000	1.0000	1.000E+00
WM36	orangered4	10	0.240	0.220	-0.430	0.446	0.488	0.165	0.8110	0.7810	0.4130	0.4125	1.0000	1.0000	1.0000	1.000E+00
WM18	orange	26	-0.200	0.590	-0.320	0.524	0.0425	0.303	0.8060	0.4250	0.6060	0.425	1.0000	1.980E-12	1.0000	1.980E-12
WM28	blue	200	-0.190	-0.260	0.410	0.552	0.411	0.183	0.8180	0.8220	0.4310	0.4306	1.0000	6.169E-12	0.4509	6.169E-12
WM39	steelblue	20	0.180	0.230	-0.370	0.58	0.47	0.232	0.8000	0.7830	0.5160	0.5156	1.0000	5.782E-01	1.0000	5.782E-01
WM31	brown	177	0.510	-0.280	-0.240	0.0904	0.381	0.446	0.5170	0.8470	0.6610	0.5166	3.524E-55	1.0000	1.0000	3.524E-55
WM12	purple	78	-0.160	0.520	-0.300	0.609	0.0827	0.344	0.7860	0.5510	0.6250	0.5513	1.0000	5.606E-27	2.834E-06	5.606E-27
WM21	black	101	-0.120	0.460	-0.290	0.701	0.129	0.364	0.7380	0.5730	0.6330	0.5733	3.139E-07	1.570E-32	1.0000	1.570E-32
WM14	magenta	86	-0.180	-0.190	0.340	0.571	0.549	0.275	0.8160	0.7840	0.5790	0.5789	1.0000	1.0000	1.962E-13	1.962E-13
WM4	darkturquoise	31	-0.150	-0.200	0.320	0.636	0.542	0.314	0.7710	0.8030	0.5980	0.5981	1.0000	1.0000	0.8119	8.119E-01
WM22	darkolivegreen	18	-0.250	0.470	-0.180	0.438	0.121	0.578	0.8340	0.6050	0.7460	0.605	1.0000	1.0000	1.0000	1.000E+00
WM3	royalblue	36	-0.330	0.063	0.260	0.289	0.845	0.408	0.6080	0.8890	0.6530	0.6084	1.0000	1.0000	0.6529	6.529E-01
WM27	yellowgreen	15	0.350	-0.170	-0.180	0.264	0.593	0.567	0.6210	0.7910	0.7560	0.6212	1.0000	1.0000	1.0000	1.000E+00
WM5	lightyellow	36	-0.160	-0.140	0.280	0.613	0.659	0.377	0.7660	0.8240	0.6280	0.6283	1.0000	9.873E-02	0.0334	3.343E-02
WM34	grey60	47	0.360	-0.260	-0.120	0.253	0.421	0.718	0.6330	0.8020	0.8210	0.6325	1.144E-07	1.0000	0.0017	1.144E-07
WM37	red	105	-0.230	0.480	-0.210	0.479	0.111	0.517	0.8330	0.6340	0.7390	0.6343	1.0000	2.292E-45	1.0000	2.292E-45
WM6	midnightblue	47	-0.360	0.380	0.008	0.248	0.217	0.98	0.6610	0.8680	0.9800	0.6613	1.0000	2.865E-01	0.0065	6.493E-03
WM26	yellow	175	0.370	-0.260	-0.120	0.241	0.41	0.71	0.6890	0.8630	0.8350	0.6886	1.249E-21	1.0000	1.0000	1.249E-21
WM30	salmon	63	0.380	-0.250	-0.140	0.229	0.434	0.664	0.7050	0.7550	0.8050	0.7046	3.605E-07	1.0000	1.0000	3.605E-07
WM15	paleturquoise	20	-0.018	0.250	-0.210	0.957	0.426	0.521	0.9570	0.7750	0.7190	0.7186	2.527E-01	1.0000	1.0000	2.527E-01
WM16	white	20	-0.130	0.300	-0.140	0.695	0.348	0.664	0.7510	0.9940	0.8300	0.7514	1.0000	7.272E-01	1.0000	7.272E-01
WM40	grey	13	-0.140	0.120	0.030	0.665	0.715	0.927	0.7600	0.8170	0.9760	0.76	1.0000	1.0000	1.0000	1.000E+00
WM29	skyblue3	12	0.130	-0.160	0.015	0.694	0.63	0.964	0.7710	0.8130	0.9890	0.7711	1.0000	1.0000	1.0000	1.000E+00
WM13	darkgreen	34	0.210	-0.280	0.043	0.507	0.377	0.895	0.8110	0.9430	0.9680	0.8112	0.2536	1.0000	0.0140	1.402E-02
WM7	green	115	-0.074	-0.033	0.100	0.82	0.918	0.758	0.8410	0.9420	0.8420	0.841	3.243E-07	1.611E-04	0.8454	3.243E-07

Table S2. The results of STRING functional enrichment analysis for the six WGCNA modules significant to the individual subtypes: A) MPA (WM23 and WM11), B) SPA, (WM1 and WM2), and C) LPA (WM25 and WM33). The top 20 pathways of biological process (GO) and Reactome pathways with a strength higher than 0.8 are presented in the order of significance by FDR. Strength (Log10 (observed/expected)) is a measure of the enrichment effect, that is the ratio between i) the number of proteins in a network that is annotated with a term and ii) the number of proteins expected to be annotated with this term in a random network of the same size.

Module ID (color)	(term ID) term description	observed gene count	background gene count	strength	false discovery rate
WM23 (darkgrey)	GO Biological process				
	(GO:0002474) Antigen processing and presentation of peptide antigen via mhc class i	6	96	1.56	2.60E-04
	(GO:0006886) Intracellular protein transport	12	999	0.84	2.60E-04
	(GO:0002478) Antigen processing and presentation of exogenous peptide antigen	6	174	1.3	0.0011
	(GO:0006521) Regulation of cellular amino acid metabolic process	4	64	1.56	0.0049
	(GO:0002479) Antigen processing and presentation of exogenous peptide antigen via mhc class i, tap-dependent	4	75	1.49	0.0069
	(GO:1902036) Regulation of hematopoietic stem cell differentiation	4	74	1.49	0.0069
	(GO:0061418) Regulation of transcription from rna polymerase ii promoter in response to hypoxia	4	78	1.47	0.007
	(GO:0038061) NIK/NF-kappaB signaling	4	81	1.45	0.0074
	(GO:0031145) Anaphase-promoting complex-dependent catabolic process	4	83	1.44	0.0075
	(GO:0043488) Regulation of mrna stability	5	183	1.2	0.0081
	(GO:0090090) Negative regulation of canonical wnt signaling pathway	5	183	1.2	0.0081
	(GO:0010972) Negative regulation of g2/m transition of mitotic cell cycle	4	92	1.4	0.009
	(GO:0010389) Regulation of g2/m transition of mitotic cell cycle	5	198	1.16	0.0091
	(GO:0031146) SCF-dependent proteasomal ubiquitin-dependent protein catabolic process	4	93	1.39	0.0091
	(GO:0010498) Proteasomal protein catabolic process	6	345	1	0.0094
	(GO:0060071) Wnt signaling pathway, planar cell polarity pathway	4	96	1.38	0.0094
	(GO:0070498) interleukin-1-mediated signaling pathway	4	96	1.38	0.0094
	(GO:0000165) MAPK cascade	6	370	0.97	0.0119
	(GO:0002223) Stimulatory c-type lectin receptor signaling pathway	4	111	1.32	0.0128
	(GO:0006839) Mitochondrial transport	5	225	1.11	0.0128
WM23 (darkgrey)	Reactome pathways				
	(HSA-450531) Regulation of mRNA stability by proteins that bind AU-rich elements	5	85	1.53	5.50E-04
	(HSA-8852276) The role of GTSE1 in G2/M progression after G2 checkpoint	5	75	1.58	5.50E-04
	(HSA-1169091) Activation of NF-kappaB in B cells	4	65	1.55	7.80E-04
	(HSA-1234176) Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha	4	63	1.56	7.80E-04
	(HSA-1236974) ER-Phagosome pathway	4	81	1.45	7.80E-04
	(HSA-1236978) Cross-presentation of soluble exogenous antigens (endosomes)	4	48	1.68	7.80E-04
	(HSA-1280218) Adaptive Immune System	9	743	0.84	7.80E-04
	(HSA-174084) Autodegradation of Cdh1 by Cdh1:APC/C	4	61	1.58	7.80E-04
	(HSA-174113) SCF-beta-TrCP mediated degradation of Emi1	4	53	1.64	7.80E-04
	(HSA-174154) APC/C:Cdc20 mediated degradation of Securin	4	65	1.55	7.80E-04
	(HSA-174178) APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	4	71	1.51	7.80E-04
	(HSA-174184) Cdc20:Phospho-APC/C mediated degradation of Cyclin A	4	70	1.52	7.80E-04
	(HSA-180534) Vpu mediated degradation of CD4	4	50	1.66	7.80E-04
	(HSA-180585) Vif-mediated degradation of APOBEC3G	4	52	1.65	7.80E-04
	(HSA-187577) SCF(Skp2)-mediated degradation of p27/p21	4	58	1.6	7.80E-04
	(HSA-195253) Degradation of beta-catenin by the destruction complex	4	81	1.45	7.80E-04
	(HSA-202424) Downstream TCR signaling	4	91	1.4	7.80E-04
	(HSA-211733) Regulation of activated PAK-2p34 by proteasome mediated degradation	4	48	1.68	7.80E-04
	(HSA-2132295) MHC class II antigen presentation	5	120	1.38	7.80E-04
	(HSA-2467813) Separation of Sister Chromatids	5	184	1.19	7.80E-04
Module ID (color)	(term ID) term description	observed gene count	background gene count	strength	false discovery rate
WM11 (darkred)	GO Biological process				
	(GO:0006614) SRP-dependent cotranslational protein targeting to membrane	7	96	1.55	1.87E-05
	(GO:0006605) Protein targeting	9	356	1.09	8.57E-05
	(GO:0090150) Establishment of protein localization to membrane	8	267	1.17	9.06E-05
	(GO:0072594) Establishment of protein localization to organelle	9	433	1.01	2.40E-04
	(GO:0072657) Protein localization to membrane	9	495	0.95	5.30E-04
	(GO:0033365) Protein localization to organelle	10	743	0.82	0.0014
	(GO:0006518) Peptide metabolic process	8	503	0.89	0.0043
	(GO:0006413) Translational initiation	5	141	1.24	0.0059
	(GO:0005840) Ribosome	5	213	1.06	0.0167
	(GO:0022626) Cytosolic ribosome	4	97	1.3	0.0167
	(GO:0042788) Polysomal ribosome	3	32	1.66	0.0167
	(GO:0005786) Signal recognition particle, endoplasmic reticulum targeting	2	6	2.21	0.0192
	(GO:1904813) ficolin-1-rich granule lumen	4	125	1.19	0.0192
	(GO:0022625) Cytosolic large ribosomal subunit	3	56	1.42	0.0251
	(GO:0005916) Fascia adherens	2	10	1.99	0.0264
	(GO:0044391) Ribosomal subunit	4	178	1.04	0.0409
	(GO:0006412) Translation	6	366	0.9	0.0427
	(GO:0019083) Viral transcription	4	115	1.23	0.0427
	(GO:0000184) Nuclear-transcribed mrna catabolic process, nonsense-mediated decay	4	119	1.22	0.0453
	(GO:0086073) Bundle of his cell-purkinje myocyte adhesion involved in cell communication	2	6	2.21	0.0453
WM11 (darkred)	Reactome pathways				
	(HSA-1799339) SRP-dependent cotranslational protein targeting to membrane	7	110	1.49	7.74E-06
	(HSA-72766) Translation	8	289	1.13	1.40E-04
	(HSA-2408522) Selenoamino acid metabolism	5	114	1.33	0.0030
	(HSA-156827) L13a-mediated translational silencing of Ceruloplasmin expression	4	108	1.26	0.0190
	(HSA-156902) Peptide chain elongation	4	87	1.35	0.0190
	(HSA-192823) Viral mRNA Translation	4	87	1.35	0.0190
	(HSA-2408557) Selenocysteine synthesis	4	91	1.33	0.0190
	(HSA-71291) Metabolism of amino acids and derivatives	6	365	0.91	0.0190
	(HSA-72689) Formation of a pool of free 40S subunits	4	99	1.3	0.0190
	(HSA-72706) GTP hydrolysis and joining of the 60S ribosomal subunit	4	109	1.25	0.0190
	(HSA-72764) Eukaryotic Translation Termination	4	91	1.33	0.0190
	(HSA-9633012) Response of EIF2AK4 (GCN2) to amino acid deficiency	4	99	1.3	0.0190
	(HSA-975956) Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC)	4	93	1.32	0.0190
	(HSA-975957) Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	4	113	1.24	0.0190
	(HSA-193692) Regulated proteolysis of p75NTR	2	11	1.95	0.0289
	(HSA-9010553) Regulation of expression of SLITs and ROBOs	4	167	1.07	0.0340
	(HSA-6791226) Major pathway of rRNA processing in the nucleolus and cytosol	4	180	1.04	0.0409
	(HSA-205043) NRIF signals cell death from the nucleus	2	16	1.79	0.0456

Table S2. continued.

Module ID (color)	(term ID) term description	observed gene count	background gene count	strength	false discovery rate
WMI (pink)	GO Biological process				
	(GO:0006614) SRP-dependent cotranslational protein targeting to membrane	27	96	1.81	2.33E-35
	(GO:0006413) Translational initiation	29	141	1.67	3.03E-35
	(GO:0019083) Viral transcription	27	115	1.73	2.76E-34
	(GO:0000184) Nuclear-transcribed mrna catabolic process, nonsense-mediated decay	27	119	1.71	5.35E-34
	(GO:0006612) Protein targeting to membrane	28	165	1.59	2.12E-32
	(GO:0006412) Translation	32	366	1.3	3.18E-29
	(GO:0016032) Viral process	38	776	1.05	5.57E-27
	(GO:0006518) Peptide metabolic process	33	503	1.17	1.17E-26
	(GO:0034655) Nucleobase-containing compound catabolic process	28	373	1.23	1.23E-23
	(GO:0043603) Cellular amide metabolic process	34	773	1	2.74E-22
	(GO:0072594) Establishment of protein localization to organelle	28	433	1.17	4.94E-22
	(GO:1901566) Organonitrogen compound biosynthetic process	38	1346	0.81	5.86E-19
	(GO:0016071) mRNA metabolic process	29	678	0.99	3.07E-18
	(GO:0033365) Protein localization to organelle	29	743	0.95	3.31E-17
	(GO:0044271) Cellular nitrogen compound biosynthetic process	38	1522	0.75	3.4E-17
	(GO:0009057) Macromolecule catabolic process	32	1058	0.84	3.46E-16
	(GO:0006886) Intracellular protein transport	31	999	0.85	6.87E-16
	(GO:0044265) Cellular macromolecule catabolic process	30	917	0.87	6.87E-16
	(GO:0051649) Establishment of localization in cell	44	2375	0.62	7.49E-16
	(GO:0042254) Ribosome biogenesis	20	292	1.19	1.35E-15
WMI (pink)	Reactome pathways				
	(HSA-156827) L13a-mediated translational silencing of Ceruloplasmin expression	29	108	1.79	1.3E-38
	(HSA-72706) GTP hydrolysis and joining of the 60S ribosomal subunit	29	109	1.78	1.3E-38
	(HSA-156902) Peptide chain elongation	27	87	1.85	7.96E-38
	(HSA-192823) Viral mRNA Translation	27	87	1.85	7.96E-38
	(HSA-2408557) Selenocysteine synthesis	27	91	1.83	1.61E-37
	(HSA-72764) Eukaryotic Translation Termination	27	91	1.83	1.61E-37
	(HSA-975956) Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC)	27	93	1.82	1.87E-37
	(HSA-72689) Formation of a pool of free 40S subunits	27	99	1.79	7.35E-37
	(HSA-9633012) Response of EIF2AK4 (GCN2) to amino acid deficiency	27	99	1.79	7.35E-37
	(HSA-1799339) SRP-dependent cotranslational protein targeting to membrane	27	110	1.75	7.48E-36
	(HSA-168255) Influenza Infection	29	154	1.63	8.42E-36
	(HSA-975957) Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	27	113	1.74	1.23E-35
	(HSA-376176) Signaling by ROBO receptors	31	213	1.52	1.79E-35
	(HSA-9010553) Regulation of expression of SLITs and ROBOs	29	167	1.6	5.16E-35
	(HSA-71291) Metabolism of amino acids and derivatives	34	365	1.33	2.83E-33
	(HSA-6791226) Major pathway of rRNA processing in the nucleolus and cytosol	27	180	1.53	6.59E-31
	(HSA-2262752) Cellular responses to stress	35	544	1.17	3.12E-29
	(HSA-422475) Axon guidance	35	547	1.16	3.59E-29
	(HSA-5663205) Infectious disease	39	826	1.03	2.54E-28
	(HSA-8953854) Metabolism of RNA	33	659	1.06	4.1E-24

Module ID (color)	(term ID) term description	observed gene count	background gene count	strength	false discovery rate
WMI (turquoise)	GO Biological process				
	(GO:0002474) Antigen processing and presentation of peptide antigen via mhc class i	23	96	0.96	1.07E-11
	(GO:0042590) Antigen processing and presentation of exogenous peptide antigen via mhc class i	20	80	0.98	1.91E-10
	(GO:0002479) Antigen processing and presentation of exogenous peptide antigen via mhc class i, tap-dependent	19	75	0.99	5.23E-10
	(GO:0006521) Regulation of cellular amino acid metabolic process	17	64	1.01	3.44E-09
	(GO:0038061) NIK/NF-kappaB signaling	18	81	0.93	1.02E-08
	(GO:0033238) Regulation of cellular amine metabolic process	18	82	0.93	1.18E-08
	(GO:1902036) Regulation of hematopoietic stem cell differentiation	17	74	0.95	2.15E-08
	(GO:0010972) Negative regulation of g2/m transition of mitotic cell cycle	18	92	0.88	5.47E-08
	(GO:0031145) Anaphase-promoting complex-dependent catabolic process	17	83	0.9	8.92E-08
	(GO:0060071) Wnt signaling pathway, planar cell polarity pathway	18	96	0.86	9.46E-08
	(GO:0061418) Regulation of transcription from rna polymerase ii promoter in response to hypoxia	16	78	0.9	2.34E-07
	(GO:0006635) Fatty acid beta-oxidation	14	56	0.98	2.65E-07
	(GO:0009060) Aerobic respiration	16	79	0.89	2.65E-07
	(GO:0031146) SCF-dependent proteasomal ubiquitin-dependent protein catabolic process	17	93	0.85	3.14E-07
	(GO:0070498) interleukin-1-mediated signaling pathway	17	96	0.83	4.57E-07
	(GO:0006614) SRP-dependent cotranslational protein targeting to membrane	16	96	0.81	2.23E-06
	(GO:0010499) Proteasomal ubiquitin-independent protein catabolic process	8	22	1.15	3.87E-05
	(GO:0006090) Pyruvate metabolic process	12	69	0.83	5.87E-05
	(GO:0002181) Cytoplasmic translation	12	72	0.81	8.58E-05
	(GO:0051238) Sequestering of metal ion	6	11	1.32	1.50E-04
WMI (turquoise)	Reactome pathways				
	(HSA-9010553) Regulation of expression of SLITs and ROBOs	32	167	0.87	3.51E-14
	(HSA-5678895) Defective CFTR causes cystic fibrosis	19	59	1.09	1.13E-11
	(HSA-5619084) ABC transporter disorders	20	75	1.01	4.44E-11
	(HSA-450408) AUF1 (hnRNP D0) binds and destabilizes mRNA	17	53	1.09	1.87E-10
	(HSA-5362768) Hh mutants are degraded by ERAD	17	54	1.08	2.12E-10
	(HSA-4641258) Degradation of DVL	17	55	1.07	2.43E-10
	(HSA-1236978) Cross-presentation of soluble exogenous antigens (endosomes)	16	48	1.11	3.73E-10
	(HSA-211733) Regulation of activated PAK-2p34 by proteasome mediated degradation	16	48	1.11	3.73E-10
	(HSA-382556) ABC-family proteins mediated transport	21	101	0.9	3.73E-10
	(HSA-5676590) NIK-->noncanonical NF-kB signaling	17	57	1.06	3.73E-10
	(HSA-5607761) Dectin-1 mediated noncanonical NF-kB signaling	17	58	1.05	3.77E-10
	(HSA-350562) Regulation of ornithine decarboxylase (ODC)	16	49	1.1	3.98E-10
	(HSA-162909) Host Interactions of HIV factors	23	129	0.84	4.73E-10
	(HSA-180534) Vpu mediated degradation of CD4	16	50	1.09	4.73E-10
	(HSA-349425) Autodegradation of the E3 ubiquitin ligase COP1	16	50	1.09	4.73E-10
	(HSA-69601) Ubiquitin Mediated Degradation of Phosphorylated Cdc25A	16	50	1.09	4.73E-10
	(HSA-72737) Cap-dependent Translation Initiation	22	116	0.86	4.73E-10
	(HSA-75815) Ubiquitin-dependent degradation of Cyclin D	16	50	1.09	4.73E-10
	(HSA-180585) Vif-mediated degradation of APOBEC3G	16	52	1.07	5.92E-10
	(HSA-8941858) Regulation of RUNX3 expression and activity	16	52	1.07	5.92E-10

Table S2. continued.

Module ID (color)	(term ID) term description	observed gene count	background gene count	strength	false discovery rate
WM25 (cyan)	GO Biological process				
	(GO:1900740) Positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway	4	27	1.7	0.0025
	(GO:2000427) Positive regulation of apoptotic cell clearance	3	8	2.1	0.0032
	(GO:0006397) mRNA processing	9	468	0.81	0.0054
	(GO:0045861) Negative regulation of proteolysis	8	356	0.88	0.0055
	(GO:0046031) ADP metabolic process	4	49	1.44	0.0068
	(GO:2001235) Positive regulation of apoptotic signaling pathway	6	180	1.05	0.0068
	(GO:0008380) RNA splicing	8	396	0.83	0.0081
	(GO:0000398) mRNA splicing, via spliceosome	7	294	0.9	0.0094
	(GO:0030449) Regulation of complement activation	4	56	1.38	0.0094
	(GO:2001233) Regulation of apoptotic signaling pathway	8	409	0.82	0.0094
	(GO:0052548) Regulation of endopeptidase activity	8	418	0.81	0.01
	(GO:0032388) Positive regulation of intracellular transport	6	223	0.96	0.0135
	(GO:0007006) Mitochondrial membrane organization	5	137	1.09	0.0139
	(GO:0071475) Cellular hyperosmotic salinity response	2	3	2.35	0.0177
	(GO:0010951) Negative regulation of endopeptidase activity	6	248	0.91	0.019
	(GO:0032481) Positive regulation of type i interferon production	4	80	1.23	0.0198
	(GO:0071480) Cellular response to gamma radiation	3	31	1.51	0.0232
	(GO:0002888) Positive regulation of myeloid leukocyte mediated immunity	3	35	1.46	0.0301
	(GO:0002735) Positive regulation of myeloid dendritic cell cytokine production	2	6	2.05	0.0355
	(GO:0006958) Complement activation, classical pathway	3	38	1.43	0.0355
	Reactome pathways				
	(HSA-111447) Activation of BAD and translocation to mitochondria	4	15	1.95	3.50E-04
	(HSA-69473) G2/M DNA damage checkpoint	6	78	1.41	3.50E-04
	(HSA-69481) G2/M Checkpoints	7	149	1.2	3.50E-04
	(HSA-75035) Chk1/Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex	4	13	2.02	3.50E-04
	(HSA-3700989) Transcriptional Regulation by TP53	9	363	0.92	5.90E-04
	(HSA-5625740) RHO GTPases activate PKNs	5	63	1.43	5.90E-04
	(HSA-69620) Cell Cycle Checkpoints	8	269	1	5.90E-04
	(HSA-174577) Activation of C3 and C5	3	7	2.16	7.20E-04
	(HSA-9614399) Regulation of localization of FOXO transcription factors	3	12	1.93	0.0021
	(HSA-977606) Regulation of Complement cascade	4	47	1.46	0.0028
	(HSA-5357801) Programmed Cell Death	6	185	1.04	0.0031
	(HSA-71406) Pyruvate metabolism and Citric Acid (TCA) cycle	4	55	1.39	0.0033
	(HSA-69206) G1/S Transition	5	129	1.12	0.0049
	(HSA-166663) Initial triggering of complement	3	22	1.66	0.0051
	(HSA-9614085) FOXO-mediated transcription	4	65	1.32	0.0051
	(HSA-1445148) Translocation of SLC2A4 (GLUT4) to the plasma membrane	4	70	1.29	0.0061
	(HSA-5633007) Regulation of TP53 Activity	5	159	1.03	0.0103
	(HSA-5628897) TP53 Regulates Metabolic Genes	4	87	1.19	0.0122
	(HSA-109581) Apoptosis	5	173	0.99	0.0137
	(HSA-70263) Gluconeogenesis	3	34	1.47	0.0137
WM33 (greenyellow)	GO Biological process				
	(GO:0098800) Inner mitochondrial membrane protein complex	8	131	1.25	5.74E-06
	(GO:0005198) Structural molecule activity	15	635	0.84	1.22E-05
	(GO:0062023) Collagen-containing extracellular matrix	11	396	0.91	2.05E-05
	(GO:0098803) Respiratory chain complex	6	80	1.34	6.75E-05
	(GO:0005746) Mitochondrial respirasome	6	84	1.32	7.08E-05
	(GO:0005747) Mitochondrial respiratory chain complex i	5	48	1.48	1.00E-04
	(GO:1990204) Oxidoreductase complex	6	107	1.21	1.70E-04
	(GO:0005201) Extracellular matrix structural constituent	7	119	1.23	3.90E-04
	(GO:0006120) Mitochondrial electron transport, nadh to ubiquinone	6	49	1.55	4.10E-04
	(GO:0022904) Respiratory electron transport chain	7	107	1.28	7.70E-04
	(GO:0008137) NADH dehydrogenase (ubiquinone) activity	5	46	1.5	8.90E-04
	(GO:0006119) Oxidative phosphorylation	7	118	1.24	9.70E-04
	(GO:0046034) ATP metabolic process	8	204	1.06	0.0018
	(GO:0006091) Generation of precursor metabolites and energy	10	405	0.86	0.0022
	(GO:0032981) Mitochondrial respiratory chain complex i assembly	5	66	1.34	0.0051
	(GO:0018149) Peptide cross-linking	4	34	1.54	0.0083
	(GO:0030280) Structural constituent of skin epidermis	3	14	1.8	0.0101
	(GO:0042135) Neurotransmitter catabolic process	3	11	1.9	0.0113
	(GO:0005200) Structural constituent of cytoskeleton	5	104	1.15	0.0124
	(GO:0070268) Cornification	5	113	1.11	0.0316
	Reactome pathways				
	(HSA-163200) Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	7	125	1.21	3.60E-04
	(HSA-611105) Respiratory electron transport	6	101	1.24	0.0013
	(HSA-6799198) Complex I biogenesis	5	55	1.42	0.0013
	(HSA-2129379) Molecules associated with elastic fibres	4	38	1.49	0.0046
	(HSA-1474244) Extracellular matrix organization	7	301	0.83	0.023
	(HSA-6809371) Formation of the cornified envelope	5	127	1.06	0.023
	(HSA-1474228) Degradation of the extracellular matrix	5	140	1.02	0.0298
	(HSA-216083) Integrin cell surface interactions	4	85	1.14	0.048

• **Figure S1.** 1,293 lung cancer patients were pathologically confirmed and received surgical operations between January 2008 to April 2022. at the St Marianna University School of Medicine Hospital (Kawasaki, Kanagawa, Japan) A) The proportions of subtypes were LPA (14%), MPA (1%), SPA (4%), and others (81%). B) The SPA cases showed a worse overall survival (OS) compared with the LPA cases (log-rank test: $p = 3.06 \times 10^{-5}$), whereas the MPA cases were not statistically significant due to the limited number of cases against the LPA and SPA cases.

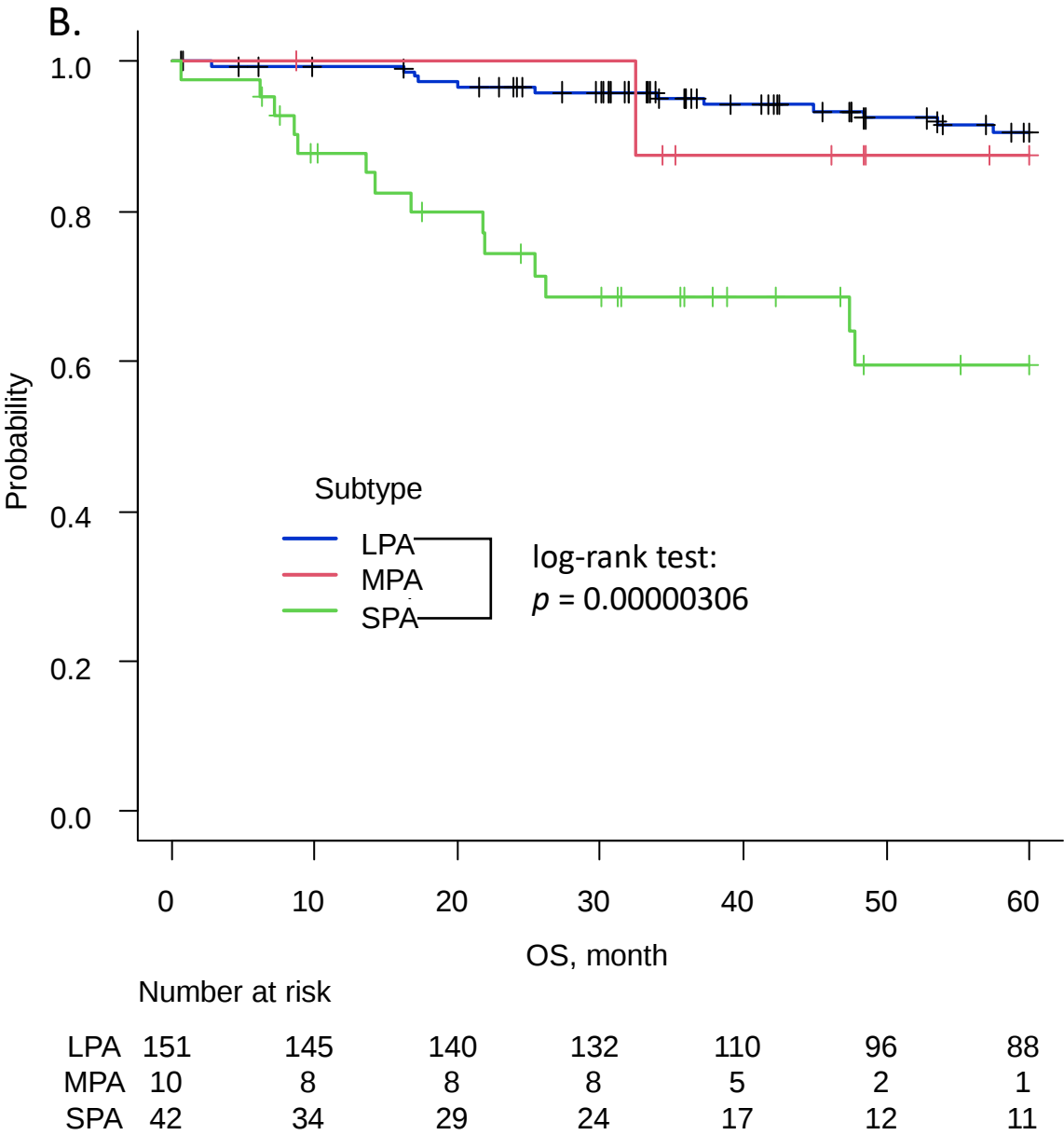
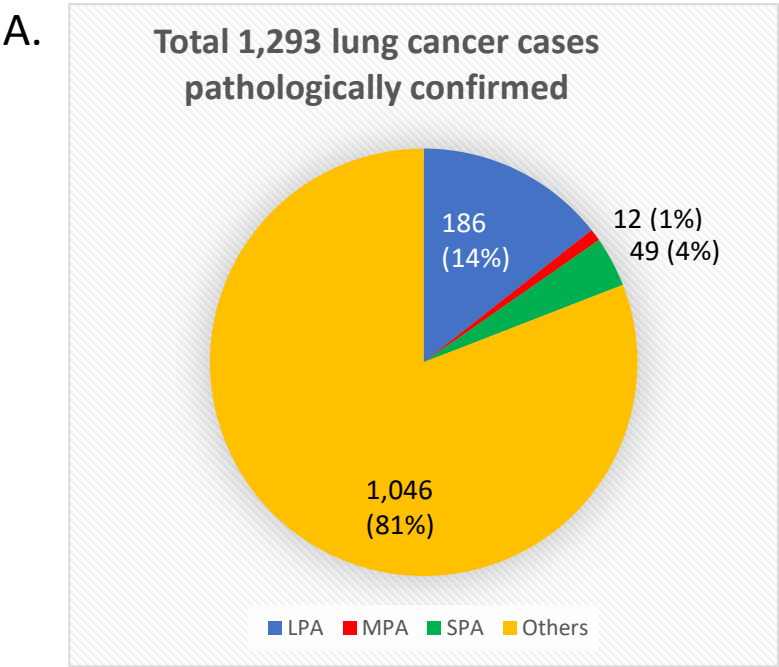
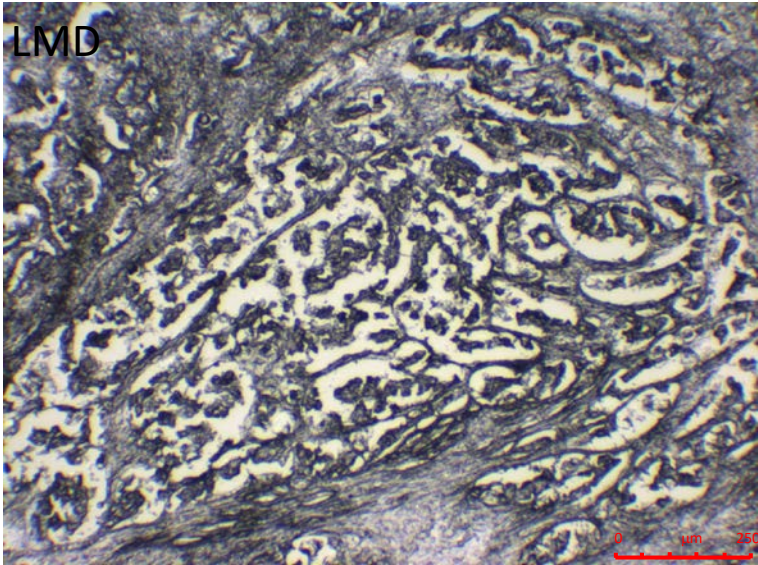


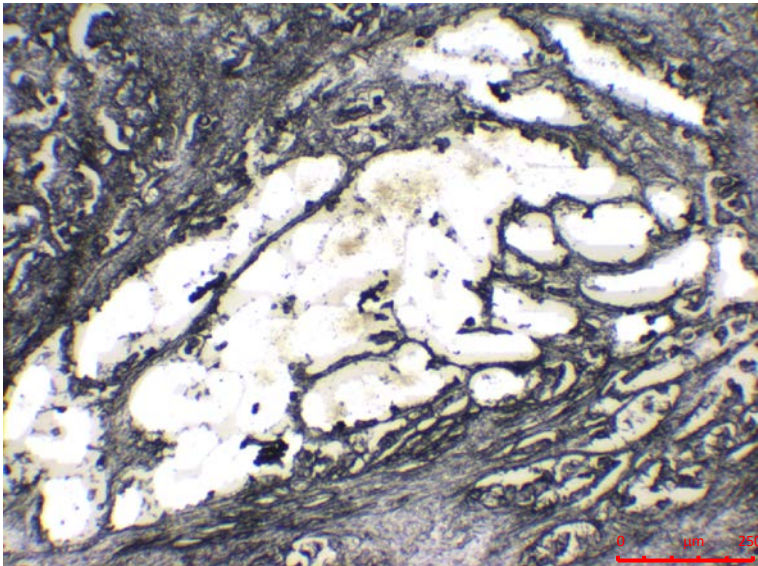
Figure S2. Representative images of tumor tissues from lung micropapillary and solid predominant adenocarcinomas (MPA and SPA) stained with hematoxylin using standard histological methods prior to laser microdissection (LMD). A) MPA (sample MPA_T69), B) SPA (sample SPA_T19). Scale bars in red color are indicated at the bottom right.

A.

Before LMD

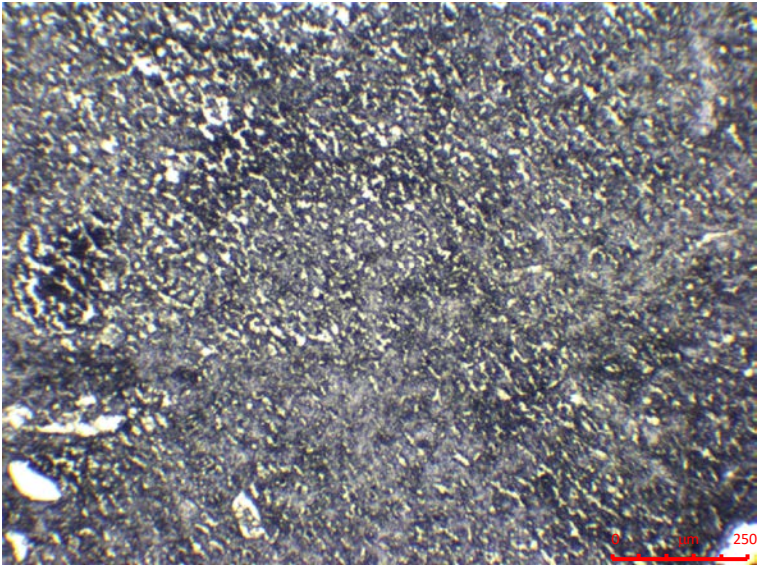


After LMD



B.

Before



After LMD

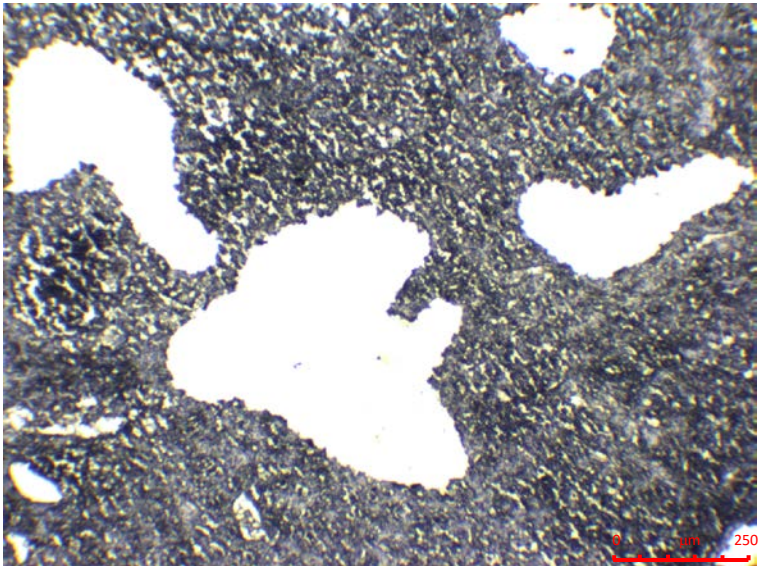
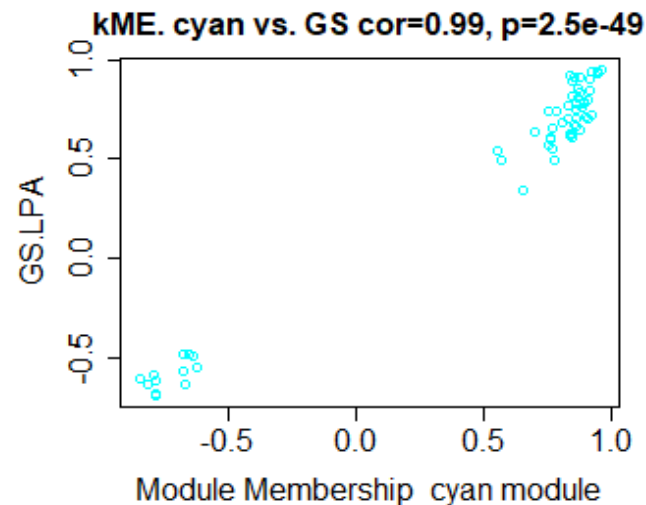
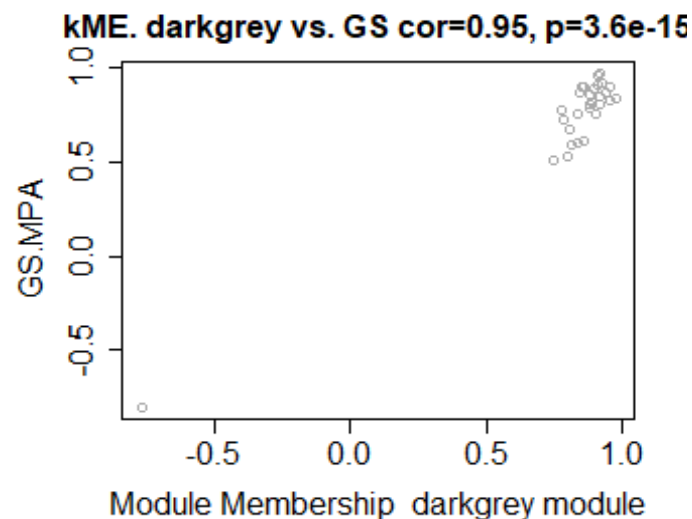


Figure S3. The module membership of module proteins (kME vs gene/protein significance) for six WGCNA modules

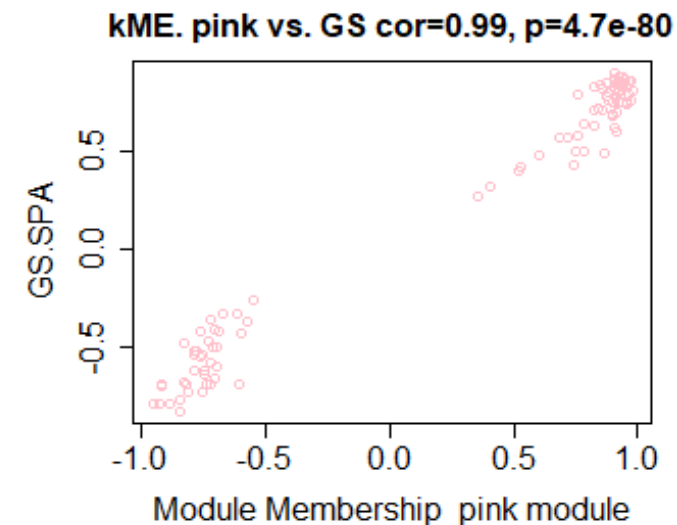
A. WM25 (cyan)



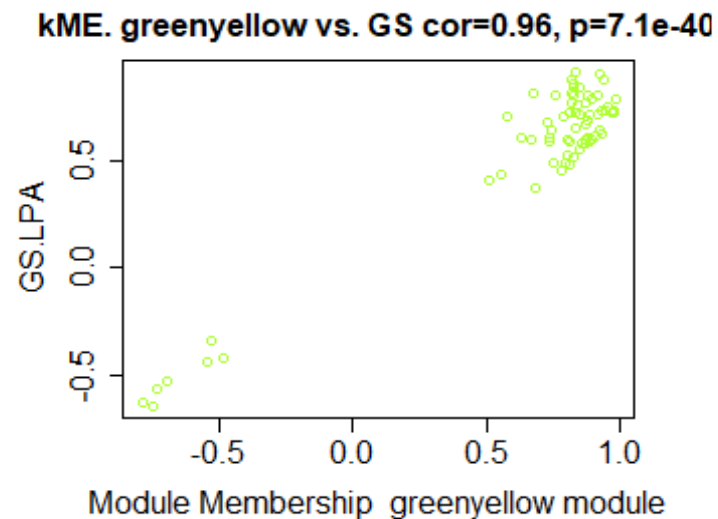
C. WM23 (cyan)



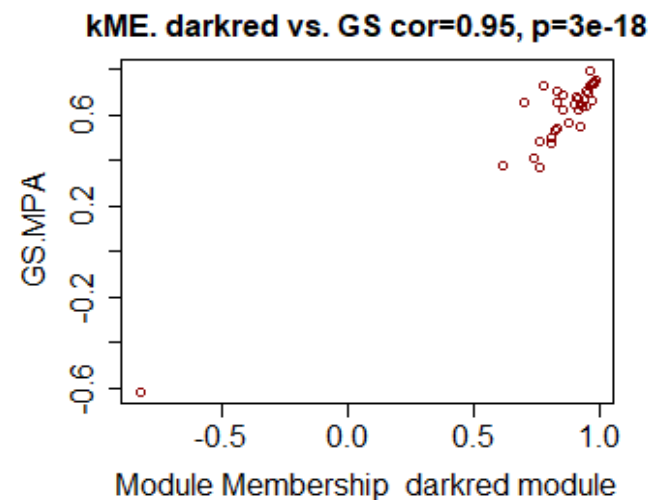
E. WM1 (pink)



B. WM33 (green-yellow)



D. WM11 (dark-red)



D. WM21 (turquoise)

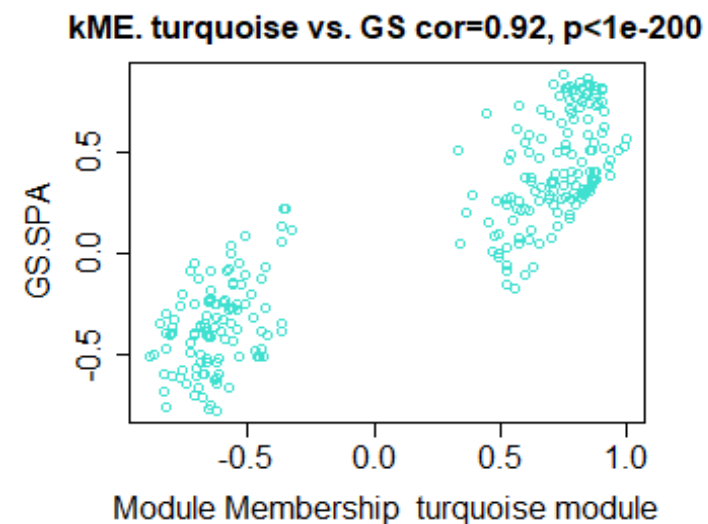


Figure S4. The Kaplan-Meier plots for MYOF and HLA-G.

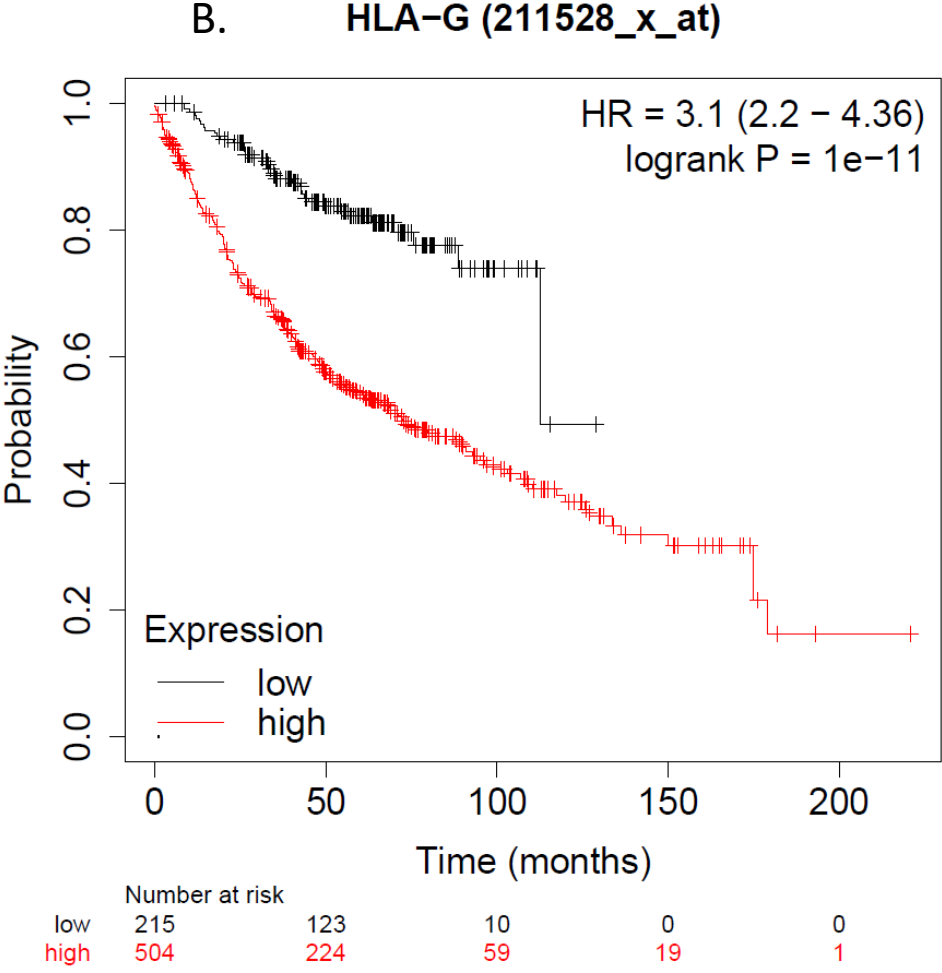
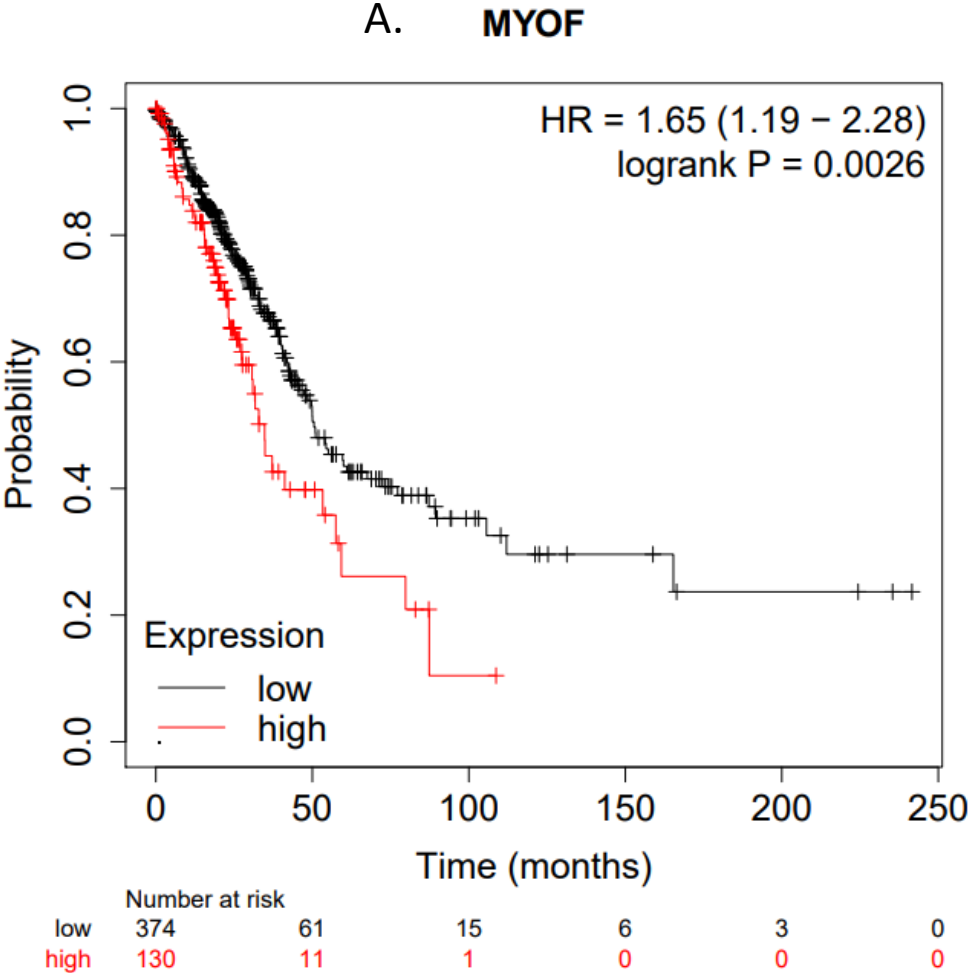
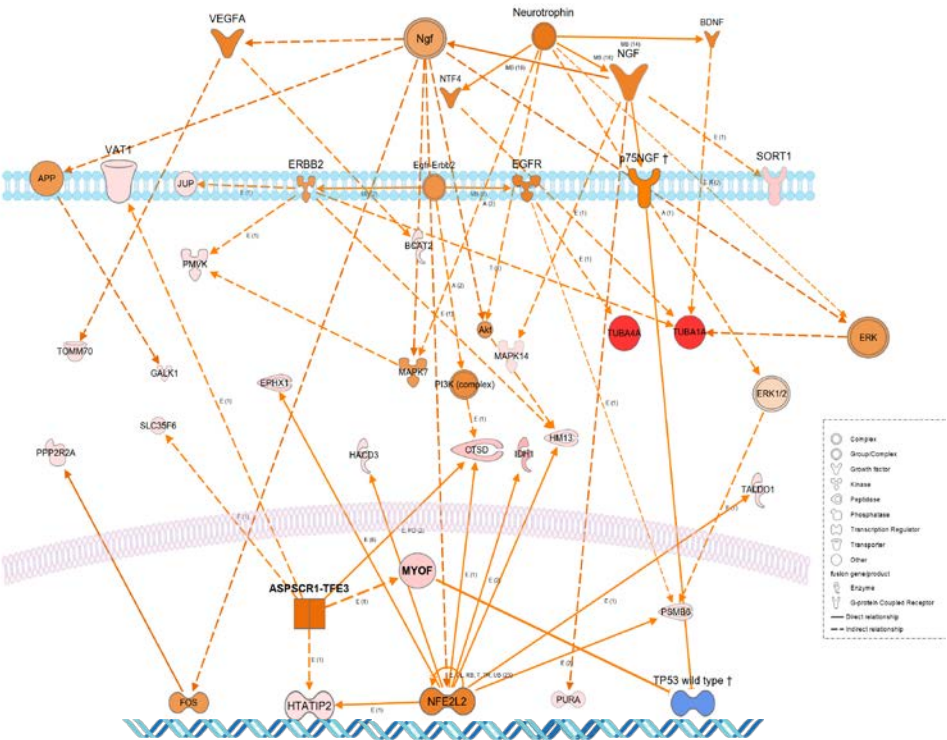


Figure S5. Genomic alteration landscape of early-stage LPA, MPA. And SPA, obtained from lung adenocarcinoma (MSKCC, 2020) database: *n* = 604). The percentage of samples with genomic alterations is presented at the left of each subtype column.



Figure S6. An integrative network of representative upstream and master regulators, along with their target molecules in datasets, as predicted for A) the combined module, WM11 (dark-red) plus WM23 (dark-grey), and B) WM1 (pink) module, significant to the MPA and SPA subtypes, respectively.

A.



B.

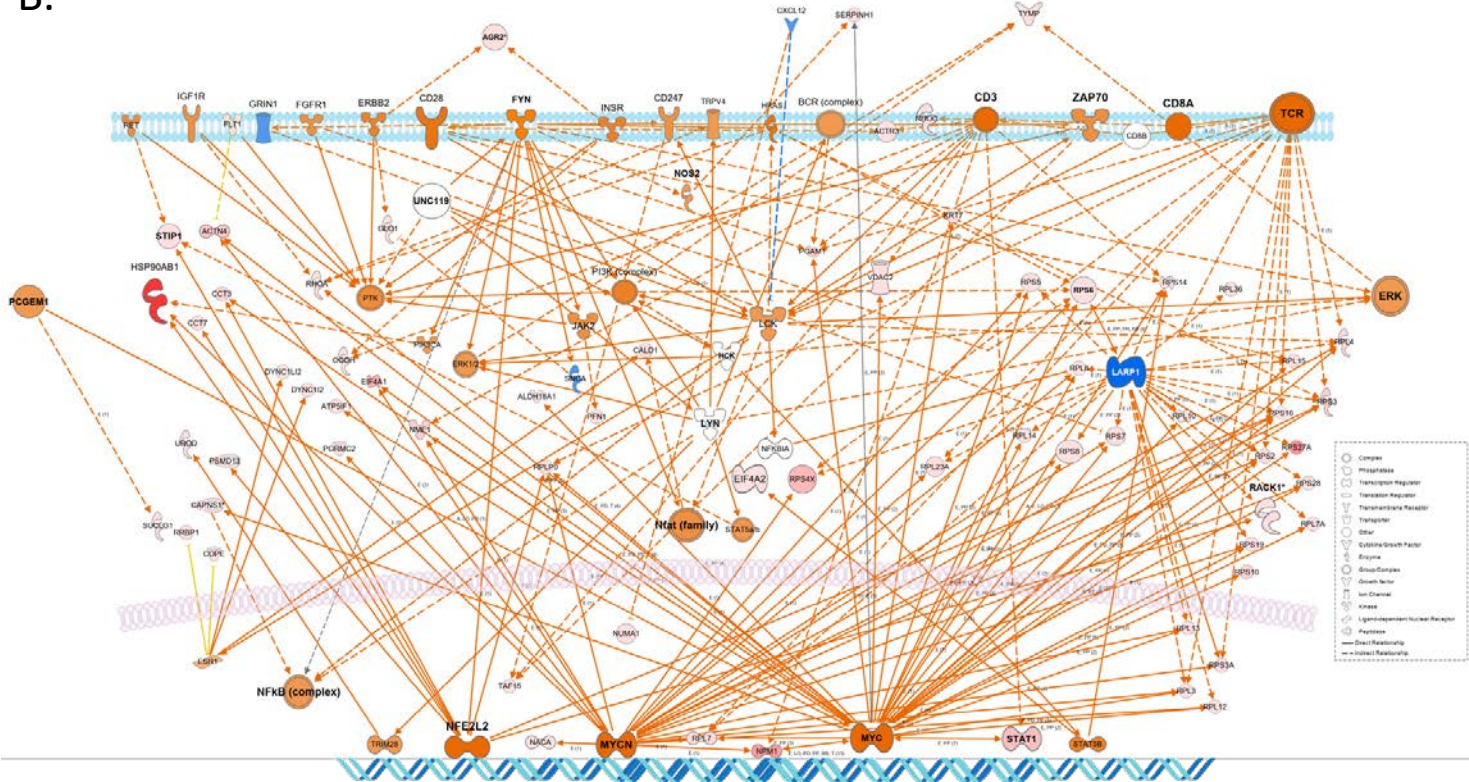


Figure S6. Continued. An integrative network of representative upstream and master regulators, along with their target molecules in datasets, as predicted for C) WM2 (turquoise) module, significant to the SPA subtype.

