

Table S3 - The top 20 dysfunctional gene sets in lung cancer.

Rank	GO term	Lung cancer associated mRNA	Lung cancer associated microRNA	Lung cancer associated methylation	Relationships among mRNA, microRNA and methylation in lung cancer
1	GO:0048585_negative regulation of response to stimulus	TNF-a[1], IL8[2], NFKBIA, NFKBID, SFRP1, WWOX, SLIT2[3]	hsa-miR-125a-3p, hsa-miR-155[4], hsa-let-7a, hsa-miR-200b/c, hsa-miR-205[5, 6], hsa-miR-29 a/b/c[7]	IL8, SFRP1, SLIT2	The enforced expression of miR-29s in lung cancer cell can restore normal patterns of DNA methylation, induces reexpression of methylation -silenced tumor suppressor genes, such as FHIT and WWOX, and inhibits tumorigenicity[7]
2	GO:0007517_muscle organ development	CHRNA1, ERBB2, TWIST1[8]	hsa-miR-125a-3p, hsa-miR-155[9], hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	ERBB2, TWIST1	
3	GO:0048514_blood vessel morphogenesis	ERBB2, CDH13, SFRP1, EGFL7, VEGFA, SLIT2	Hsa-miR-375, hsa-miR-34b, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	ERBB2, SFRP1, SLIT2	Promoters of miR-34b, EGFL7 are methylation, up regulate c-Met and Crk expressions[10]
4	GO:0051146_striated muscle cell differentiation	CHRNA1, ERBB2	hsa-miR-125a-3p, hsa-miR-155	ERBB2	
5	GO:0001525_angiogenesis	VEGFC[11], IL8, ERBB2, CDH13, SFRP1, EGFL7, VEGFA, SLIT2	Hsa-miR-375, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	IL8, ERBB2, CDH13, SFRP1, SLIT2	
6	GO:0045595_regulation of cell differentiation	VEGFC, NFKB1, NFKBIA, NFKBID, TNF, KEAP1, CHRNA3, ERBB2, CDKN2A, FAS, NEUROD1, CDX2, SFRP1, TWIST1, DNMT3B, SLIT2	hsa-miR-125a-5p, hsa-miR-125a-3p, hsa-miR-34b, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29 a/b/c[12]	NFKB1[1], TNF, ERBB2, CDKN2A, FAS, NEUROD1, SFRP1, TWIST1, CALCA, DNMT3B, SLIT2[13, 14]	miR-200c was silenced by methylation and down regulated TCF8 and E-cadherin, which result in cancer invasion and deterioration[5]; up regulation of miR-29 make sure normal patterns of DNA methylation, induces reexpression of methylation silenced tumor suppressor genes, such as FHIT and WWOX[7]
7	GO:0007162_negative regulation of cell adhesion	CDKN2A, CDH13	hsa-let-7a, hsa-miR-200b/c	CDKN2A, CDH13, CDH1	
8	GO:0060191_regulation of lipase activity		hsa-miR-34b, hsa-miR-200c, hsa-miR-205	CALCA	
9	GO:0006275_regulation of DNA replication		hsa-miR-125a-5p, hsa-let-7a, hsa-miR-200b/c, hsa-miR-29b/c		
10	GO:0061061_muscle structure development	CHRNA1, ERBB2,	hsa-miR-125a-3p, hsa-miR-34b,	ERBB2, TWIST1	

		TWIST1	hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c		
11	GO:0022008_neurogenesis	ASH1 YAP1, VEGFC, CHRNA1, ERBB2, KRAS, DAPK3, FAS, NEUROD1/2,OP CML, TWIST1, CDH1, DNMT3B, NAB2, SLIT2	hsa-miR-125a-5p, hsa-miR-34b, hsa-miR-155, hsa-let-7a, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	ERBB2, KRAS, DAPK3, FAS, OPCML, TWIST1, CDH1, DNMT3B, SLIT2[13, 14]	miR-34b methylation up regulates c-Met[10]; Methylation makes miR-200c silence and down regulates TCF8 expression, then results in E-cadherin low expression, promote tumor deteriorate[5]
13	GO:0008543_fibroblast growth factor receptor signaling pathway		hsa-miR-200b/c, hsa-miR-29a/b/c		
13	GO:0035107_appendage morphogenesis	HOXA9, TWIST1	hsa-miR-125a-5p, hsa-miR-34b, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	HOXA9, TWIST1	
13	GO:0035108_limb morphogenesis	COX-2, VEGFC, HOXA9, TWIST1	hsa-miR-125a-5p, hsa-miR-34b, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	HOXA9, TWIST1	
15	GO:0001568_blood vessel development	VEGFC, IL8, ERBB2, CDH13, CDX2, SFRP1, EGR1, VEGFA, SLIT2	hsa-miR-34b, hsa-miR-155, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	IL8, ERBB2, CDH13, CDX2, SFRP1, SLIT2	In lung cancer cells, EGR1 activates VEGFA expression[11]
16	GO:0005576_extracellular region	VEGFC, IL8, TNF, FAS, TIMP3 , LAMA3 , LAMB3 , LAMC2 , TMEFF2, CDH13, SFRP1, EGFL7, KLK13, MMP1, VEGFA, SLIT2[8, 11, 15]	hsa-miR-125a-5p, hsa-miR-125a-3p, hsa-miR-34b, hsa-miR-155, hsa-let-7a, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	IL8, TNF, FAS, TIMP3 , TMEFF2, CDH13, SFRP1, CALCA, MMP1, SLI[15]	miR-200c was silenced by methylation, down regulated TCF8 and E-cadherin, involving in lung cancer deteriorate[6]. KLK13 was up regulated by demethylation in its promoter, involving in tumor invasion; SLIT2 low expression can down regulate beta-catenin and E-cadherin[16].
17	GO:0050793_regulation of developmental process	VEGFC, NFKB1, NFKBIA, NFKBID,	hsa-miR-125a-5p, hsa-miR-125a-3p, hsa-miR-34b, hsa-miR-155,	NFKB1, TNF, ERBB2, CDKN2A ,	Up regulation of miR-29make sure normal patterns of DNA methylation, induces reexpression of methylation -silenced tumor suppressor

		TNF, KEAP1, CHRNA1, ERBB2, CDKN2A , FAS, LAMA3 , NEUROD1, CDX2, SFRP1, TWIST1, DNMT3B, VEGFA, SLIT2[11, 17]	hsa-miR-200b/c, hsa-miR-205, hsa-miR-29 a/b/c[7, 12]	FAS, LAMA3 , SFRP1, TWIST1, CALCA, CDH1, DNMT3B, SLIT2[14]	genes, such as FHIT and WWOX[7]
18.5	GO:0010648_negative regulation of cell communication	NFKBIA, NFKBID, SFRP1, WWOX, SLIT2	hsa-miR-125a-3p, hsa-miR-155, hsa-let-7a, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	SFRP1, SLIT2	Up regulation of miR-29 make sure normal patterns of DNA methylation, induces reexpression of methylation silenced tumor suppressor genes, such as FHIT and WWOX[7]
18.5	GO:0023057_negative regulation of signaling	NFKBIA, NFKBID, SFRP1, WWOX, SLIT2	hsa-miR-125a-3p, hsa-miR-155, hsa-let-7a, hsa-miR-200b/c, hsa-miR-205, hsa-miR-29a/b/c	SFRP1, SLIT2	
20	GO:0019216_regulation of lipid metabolic process	NFKB1, TNF		NFKB1, TNF	

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