

Supplemental information

Targeting a miRNA–mRNA Regulatory Network to Overcome Radioresistance in Head and Neck Cancer: Identification of I-OMe-AG-538 via Transcriptome-Guided Drug Repurposing

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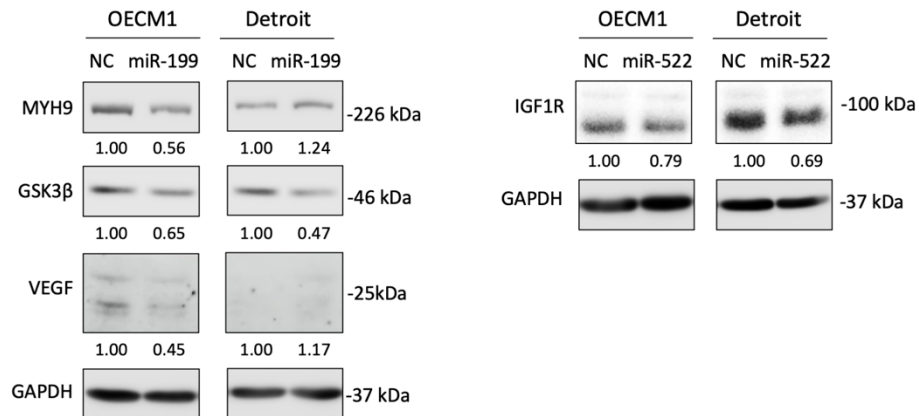
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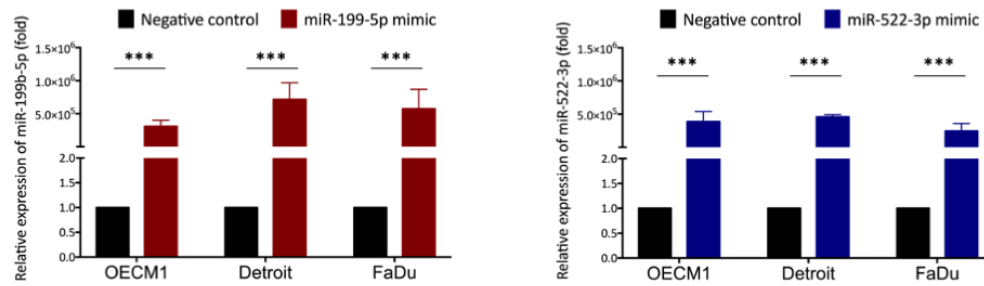
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Supplementary Figure S1



Supplementary Figure S1. Western blot validation of hub TSmiR–target oncoprotein interactions in HNC cells. Western blot analyses of predicted target proteins in two HNC cell lines (OECM1 and Detroit) following transfection with hub TSmiR mimics or the non-targeting mimic controls (NC). Protein levels of MYH9, GSK3 β , and VEGFA were examined after miR-199b-5p mimic transfection (miR-199), and IGF1R protein levels were examined after miR-522-3p mimic transfection (miR-522). All blots were quantified by densitometry, normalized to GAPDH, and expressed as fold-change relative to the negative control. These results support the miRNA–mRNA interactions within the defined regulatory network.

Supplementary Figure S2



Supplementary Figure S2. Confirmation of miRNA mimic overexpression by RT-qPCR in HNC cell lines. RT-qPCR analysis of miR-199b-5p and miR-522-3p expression levels in three HNC cell lines (OECM1, FaDu, and Detroit) 48 h after transfection with the respective miRNA mimics or non-targeting miRNA mimic control (Negative control). Data are presented as mean $\pm$ SD of three independent experiments. (***, $P < 0.001$, Student's t-test).

Supplementary Table S1. List of differentially expressed miRNAs associated with the radioresistant phenotype in OECM1 cells.

miRNA	OECM1-Pt	OECM1-RR	log ₂ (RR/Pt)	Expression
hsa-miR-513a-5p	0.23	19.18	6.37	Up
hsa-miR-95-3p	0.01	0.24	4.57	Up
hsa-miR-654-5p	0.01	0.23	4.52	Up
hsa-miR-770-5p	0.01	0.23	4.08	Up
hsa-miR-551b-3p	0.01	0.12	3.61	Up
hsa-miR-631	0.01	0.11	3.48	Up
hsa-miR-328-3p	0.01	0.11	3.39	Up
hsa-miR-636	0.01	0.09	3.19	Up
hsa-miR-662	0.01	0.08	2.93	Up
hsa-miR-212-3p	0.11	0.72	2.75	Up
hsa-miR-564	0.02	0.12	2.55	Up
hsa-miR-30b-5p	0.62	3.42	2.47	Up
hsa-miR-610	0.01	0.05	2.43	Up
hsa-miR-519e-5p	0.01	0.05	2.41	Up
hsa-miR-129-5p	0.02	0.11	2.37	Up
hsa-miR-589-3p	0.01	0.05	2.35	Up
hsa-miR-9-5p	0.26	1.29	2.31	Up
hsa-miR-30c-5p	2.04	9.10	2.16	Up
hsa-miR-622	0.03	0.14	2.03	Up
hsa-miR-508-3p	0.01	0.04	1.99	Up
hsa-miR-198	0.05	0.17	1.79	Up

hsa-miR-520h	0.01	0.04	1.77	Up
hsa-miR-214-3p	0.01	0.03	1.74	Up
hsa-miR-648	0.01	0.03	1.68	Up
hsa-miR-609	0.01	0.03	1.67	Up
hsa-miR-494-3p	21.47	66.40	1.63	Up
hsa-miR-653-5p	0.01	0.03	1.62	Up
hsa-miR-572	0.15	0.45	1.61	Up
hsa-miR-637	0.01	0.03	1.57	Up
hsa-miR-302a-5p	0.03	0.09	1.57	Up
hsa-miR-638	1.68	4.83	1.52	Up
hsa-miR-517b-3p	0.01	0.03	1.49	Up
hsa-miR-138-5p	0.03	0.07	1.47	Up
hsa-miR-370-3p	2.26	6.10	1.43	Up
hsa-miR-520d-3p	0.04	0.11	1.42	Up
hsa-miR-634	0.01	0.03	1.42	Up
hsa-miR-202-3p	1.45	3.81	1.39	Up
hsa-miR-597-5p	0.01	0.03	1.39	Up
hsa-miR-504-5p	0.01	0.03	1.37	Up
hsa-miR-509-3p	0.40	1.03	1.35	Up
hsa-miR-630	0.19	0.46	1.28	Up
hsa-miR-518c-3p	0.01	0.02	1.22	Up
hsa-miR-483-3p	0.01	0.02	1.18	Up
hsa-miR-373-3p	0.05	0.11	1.18	Up
hsa-miR-605-5p	0.01	0.02	1.08	Up

hsa-miR-501-5p	0.21	0.43	1.01	Up
hsa-miR-452-5p	1.54	3.10	1.01	Up
hsa-miR-9-3p	0.96	1.92	1.01	Up
hsa-miR-142-3p	0.27	0.13	-1.00	Down
hsa-miR-520c-3p	0.03	0.02	-1.00	Down
hsa-miR-520g-3p	0.06	0.03	-1.01	Down
hsa-miR-493-5p	0.03	0.01	-1.03	Down
hsa-miR-199b-5p	0.04	0.02	-1.05	Down
hsa-miR-345-5p	1.91	0.91	-1.07	Down
hsa-miR-126-3p	2.10	0.99	-1.08	Down
hsa-miR-519c-5p	0.08	0.04	-1.08	Down
hsa-miR-649	0.04	0.02	-1.10	Down
hsa-miR-485-5p	0.03	0.01	-1.10	Down
hsa-miR-136-5p	0.02	0.01	-1.11	Down
hsa-miR-577	0.02	0.01	-1.13	Down
hsa-miR-193a-3p	0.61	0.27	-1.18	Down
hsa-miR-192-5p	3.06	1.35	-1.19	Down
hsa-miR-215-5p	1.80	0.79	-1.19	Down
hsa-miR-190a-5p	0.22	0.09	-1.21	Down
hsa-miR-147a	0.02	0.01	-1.22	Down
hsa-miR-520b-3p	0.02	0.01	-1.22	Down
hsa-miR-122-5p	0.09	0.04	-1.23	Down
hsa-miR-155-5p	6.73	2.86	-1.24	Down
hsa-miR-512-3p	0.05	0.02	-1.26	Down

hsa-miR-18b-5p	2.84	1.18	-1.27	Down
hsa-miR-382-5p	0.12	0.05	-1.30	Down
hsa-miR-519b-3p	0.08	0.03	-1.33	Down
hsa-miR-602	0.09	0.03	-1.35	Down
hsa-miR-34b-5p	1.00	0.36	-1.48	Down
hsa-miR-526b-5p	0.03	0.01	-1.49	Down
hsa-miR-548b-3p	0.03	0.01	-1.54	Down
hsa-miR-302c-3p	0.03	0.01	-1.55	Down
hsa-miR-409-5p	0.04	0.01	-1.62	Down
hsa-miR-548c-3p	0.59	0.19	-1.63	Down
hsa-miR-380-3p	0.03	0.01	-1.71	Down
hsa-miR-562	0.03	0.01	-1.80	Down
hsa-miR-571	0.05	0.01	-1.83	Down
hsa-miR-137-3p	0.04	0.01	-1.89	Down
hsa-miR-566	0.04	0.01	-1.89	Down
hsa-miR-520f-3p	0.04	0.01	-2.00	Down
hsa-miR-586	0.04	0.01	-2.02	Down
hsa-miR-34c-5p	0.71	0.17	-2.08	Down
hsa-miR-146a-5p	0.09	0.02	-2.12	Down
hsa-miR-519c-3p	0.05	0.01	-2.17	Down
hsa-miR-329-3p	0.05	0.01	-2.20	Down
hsa-miR-583	0.05	0.01	-2.25	Down
hsa-miR-573	0.05	0.01	-2.26	Down
hsa-miR-522-3p	0.05	0.01	-2.33	Down

hsa-miR-517a-3p	0.05	0.01	-2.33	Down
hsa-miR-1-3p	0.05	0.01	-2.36	Down
hsa-miR-369-5p	0.05	0.01	-2.36	Down
hsa-miR-187-3p	0.06	0.01	-2.41	Down
hsa-miR-563	0.06	0.01	-2.46	Down
hsa-miR-539-5p	0.08	0.01	-2.48	Down
hsa-miR-499a-5p	0.06	0.01	-2.51	Down
hsa-miR-299-3p	0.07	0.01	-2.59	Down
hsa-miR-302b-3p	0.06	0.01	-2.68	Down
hsa-miR-548a-3p	0.07	0.01	-2.74	Down
hsa-miR-451a	0.07	0.01	-2.76	Down
hsa-miR-302a-3p	0.10	0.01	-2.81	Down
hsa-miR-139-5p	0.20	0.03	-2.88	Down
hsa-miR-520e-3p	0.07	0.01	-2.89	Down
hsa-miR-495-3p	0.07	0.01	-2.90	Down
hsa-miR-409-3p	0.15	0.02	-2.92	Down
hsa-miR-299-5p	0.08	0.01	-2.97	Down
hsa-miR-561-3p	0.08	0.01	-3.04	Down
hsa-miR-520a-3p	0.08	0.01	-3.05	Down
hsa-miR-558	0.09	0.01	-3.19	Down
hsa-miR-379-5p	0.29	0.03	-3.36	Down
hsa-miR-369-3p	0.11	0.01	-3.52	Down
hsa-miR-553	0.12	0.01	-3.53	Down
hsa-miR-381-3p	0.12	0.01	-3.57	Down

hsa-miR-410-3p	0.21	0.01	-4.40	Down
hsa-miR-154-3p	0.23	0.01	-4.53	Down
hsa-miR-758-3p	0.24	0.01	-4.56	Down
hsa-miR-376a-3p	0.89	0.04	-4.68	Down
hsa-miR-376c-3p	0.27	0.01	-4.76	Down
hsa-miR-377-3p	0.56	0.02	-4.85	Down
hsa-miR-376b-3p	0.38	0.01	-5.24	Down

RR, radioresistance; Pt, parental

Supplementary Table S2. List of differentially expressed miRNAs associated with the radioresistant phenotype in Detroit cells.

miRNA	Detroit-Pt	Detroit-RR	log ₂ (RR/Pt)	Expression
hsa-miR-654-5p	0.05	2.56	5.69	Up
hsa-miR-373-5p	0.01	0.50	5.64	Up
hsa-miR-498-5p	0.05	1.36	4.74	Up
hsa-miR-614	0.01	0.22	4.48	Up
hsa-miR-617	0.01	0.21	4.40	Up
hsa-miR-512-3p	0.02	0.34	4.14	Up
hsa-miR-662	0.03	0.38	3.56	Up
hsa-miR-198	0.09	0.98	3.39	Up
hsa-miR-184	0.01	0.09	3.14	Up
hsa-miR-602	0.06	0.49	3.04	Up
hsa-miR-596	0.01	0.08	2.92	Up
hsa-miR-663a	0.19	1.35	2.86	Up
hsa-miR-513a-5p	2.58	17.65	2.77	Up
hsa-miR-638	2.12	14.28	2.75	Up
hsa-miR-659-3p	0.01	0.06	2.68	Up
hsa-miR-583	0.01	0.08	2.59	Up
hsa-miR-188-5p	0.99	5.91	2.57	Up
hsa-miR-622	0.10	0.54	2.48	Up
hsa-miR-422a	0.01	0.05	2.34	Up
hsa-miR-564	0.10	0.41	2.01	Up
hsa-miR-630	0.35	1.14	1.70	Up

hsa-miR-129-5p	0.04	0.12	1.62	Up
hsa-miR-431-5p	0.01	0.03	1.59	Up
hsa-miR-410-3p	0.01	0.03	1.58	Up
hsa-miR-191-3p	0.18	0.52	1.55	Up
hsa-miR-370-3p	3.69	10.63	1.53	Up
hsa-miR-572	0.62	1.73	1.48	Up
hsa-miR-629-3p	0.21	0.57	1.46	Up
hsa-miR-214-3p	0.04	0.12	1.45	Up
hsa-miR-134-5p	0.06	0.16	1.40	Up
hsa-miR-557	0.10	0.26	1.30	Up
hsa-miR-601	0.20	0.47	1.22	Up
hsa-miR-100-5p	5.16	11.90	1.21	Up
hsa-miR-125b-5p	11.10	25.11	1.18	Up
hsa-miR-206	0.20	0.46	1.17	Up
hsa-miR-492	0.03	0.06	1.15	Up
hsa-miR-658	0.06	0.12	1.08	Up
hsa-miR-301a-3p	17.15	8.54	-1.01	Down
hsa-miR-193a-3p	2.47	1.23	-1.01	Down
hsa-miR-330-3p	0.44	0.22	-1.02	Down
hsa-miR-495-3p	0.02	0.01	-1.04	Down
hsa-miR-412-3p	0.02	0.01	-1.06	Down
hsa-miR-625-5p	4.94	2.36	-1.07	Down
hsa-miR-503-5p	0.51	0.24	-1.07	Down
hsa-miR-33a-5p	13.88	6.49	-1.10	Down

hsa-miR-324-5p	5.88	2.74	-1.10	Down
hsa-miR-218-5p	0.14	0.07	-1.10	Down
hsa-miR-517c-3p	0.02	0.01	-1.13	Down
hsa-miR-199b-5p	0.02	0.01	-1.13	Down
hsa-miR-150-5p	0.02	0.01	-1.14	Down
hsa-miR-373-3p	0.16	0.07	-1.14	Down
hsa-miR-219a-5p	0.25	0.11	-1.14	Down
hsa-miR-342-3p	3.00	1.36	-1.14	Down
hsa-miR-657	0.02	0.01	-1.15	Down
hsa-miR-514a-3p	0.02	0.01	-1.16	Down
hsa-miR-508-3p	0.05	0.02	-1.16	Down
hsa-miR-151a-3p	19.67	8.71	-1.18	Down
hsa-miR-636	0.16	0.07	-1.18	Down
hsa-miR-802	0.02	0.01	-1.19	Down
hsa-miR-645	0.02	0.01	-1.19	Down
hsa-miR-484	1.45	0.63	-1.19	Down
hsa-miR-505-3p	0.14	0.06	-1.21	Down
hsa-miR-510-5p	0.04	0.02	-1.23	Down
hsa-miR-769-5p	0.40	0.17	-1.23	Down
hsa-miR-561-3p	0.02	0.01	-1.24	Down
hsa-miR-518e-3p	0.02	0.01	-1.26	Down
hsa-miR-766-3p	1.26	0.53	-1.26	Down
hsa-miR-30d-5p	18.57	7.61	-1.29	Down
hsa-miR-589-3p	0.16	0.06	-1.29	Down

hsa-miR-138-5p	0.34	0.14	-1.29	Down
hsa-miR-367-3p	0.02	0.01	-1.29	Down
hsa-miR-615-3p	0.02	0.01	-1.30	Down
hsa-miR-520d-5p	0.03	0.01	-1.35	Down
hsa-miR-525-5p	0.03	0.01	-1.35	Down
hsa-miR-25-3p	33.29	12.85	-1.37	Down
hsa-miR-154-5p	0.03	0.01	-1.41	Down
hsa-miR-576-5p	0.03	0.01	-1.42	Down
hsa-miR-519d-3p	0.03	0.01	-1.42	Down
hsa-miR-126-3p	0.39	0.15	-1.42	Down
hsa-miR-127-3p	0.03	0.01	-1.43	Down
hsa-miR-580-3p	0.03	0.01	-1.43	Down
hsa-miR-340-3p	0.15	0.06	-1.44	Down
hsa-miR-106b-5p	50.67	18.16	-1.48	Down
hsa-miR-605-5p	0.03	0.01	-1.49	Down
hsa-miR-302a-3p	0.04	0.01	-1.49	Down
hsa-miR-519b-3p	0.03	0.01	-1.50	Down
hsa-miR-599	0.03	0.01	-1.51	Down
hsa-miR-216a-5p	0.03	0.01	-1.51	Down
hsa-miR-542-5p	0.50	0.18	-1.51	Down
hsa-miR-527	0.03	0.01	-1.53	Down
hsa-miR-520c-3p	0.04	0.01	-1.54	Down
hsa-miR-378a-3p	13.60	4.61	-1.56	Down
hsa-miR-92b-3p	1.22	0.41	-1.58	Down

hsa-miR-559	0.03	0.01	-1.59	Down
hsa-miR-133b	0.03	0.01	-1.60	Down
hsa-miR-520a-3p	0.03	0.01	-1.61	Down
hsa-miR-199a-5p	0.07	0.02	-1.62	Down
hsa-miR-34b-5p	0.58	0.19	-1.62	Down
hsa-miR-122-5p	0.03	0.01	-1.66	Down
hsa-miR-378a-5p	0.41	0.13	-1.68	Down
hsa-miR-618	0.03	0.01	-1.71	Down
hsa-miR-517b-3p	0.03	0.01	-1.72	Down
hsa-miR-637	0.03	0.01	-1.72	Down
hsa-miR-93-5p	36.80	11.05	-1.74	Down
hsa-miR-656-3p	0.03	0.01	-1.75	Down
hsa-miR-548b-3p	0.03	0.01	-1.79	Down
hsa-miR-483-3p	0.03	0.01	-1.80	Down
hsa-miR-202-5p	0.04	0.01	-1.82	Down
hsa-miR-641	0.06	0.02	-1.84	Down
hsa-miR-518f-3p	0.04	0.01	-1.85	Down
hsa-miR-613	0.04	0.01	-1.86	Down
hsa-miR-519c-3p	0.04	0.01	-1.87	Down
hsa-miR-143-3p	0.04	0.01	-1.92	Down
hsa-miR-302a-5p	0.04	0.01	-1.96	Down
hsa-miR-346	0.04	0.01	-1.98	Down
hsa-miR-520d-3p	0.16	0.04	-1.99	Down
hsa-miR-595	0.38	0.10	-2.00	Down

hsa-miR-525-3p	0.04	0.01	-2.00	Down
hsa-miR-10a-5p	0.70	0.17	-2.04	Down
hsa-miR-455-5p	3.62	0.87	-2.06	Down
hsa-miR-10b-5p	0.16	0.04	-2.06	Down
hsa-miR-544a	0.04	0.01	-2.06	Down
hsa-miR-506-3p	0.04	0.01	-2.06	Down
hsa-miR-520f-3p	0.04	0.01	-2.07	Down
hsa-miR-223-3p	0.21	0.05	-2.09	Down
hsa-miR-520g-3p	0.04	0.01	-2.14	Down
hsa-miR-499a-5p	0.04	0.01	-2.14	Down
hsa-miR-299-3p	0.07	0.02	-2.17	Down
hsa-miR-551a	0.05	0.01	-2.17	Down
hsa-miR-619-3p	0.05	0.01	-2.18	Down
hsa-miR-302c-5p	0.05	0.01	-2.18	Down
hsa-miR-522-3p	0.05	0.01	-2.20	Down
hsa-miR-571	0.09	0.02	-2.23	Down
hsa-miR-517a-3p	0.05	0.01	-2.26	Down
hsa-miR-449a	0.05	0.01	-2.26	Down
hsa-miR-582-5p	0.05	0.01	-2.26	Down
hsa-miR-524-3p	0.05	0.01	-2.26	Down
hsa-miR-302d-3p	0.05	0.01	-2.29	Down
hsa-miR-661	0.05	0.01	-2.41	Down
hsa-miR-204-5p	0.05	0.01	-2.41	Down
hsa-miR-376a-5p	0.05	0.01	-2.43	Down

hsa-miR-382-5p	0.06	0.01	-2.45	Down
hsa-miR-383-5p	0.10	0.02	-2.48	Down
hsa-miR-519e-3p	0.06	0.01	-2.53	Down
hsa-miR-323b-5p	0.18	0.03	-2.57	Down
hsa-miR-449b-5p	0.06	0.01	-2.58	Down
hsa-miR-451a	0.07	0.01	-2.60	Down
hsa-miR-130a-3p	21.06	3.25	-2.70	Down
hsa-miR-302b-3p	0.07	0.01	-2.72	Down
hsa-miR-579-3p	0.07	0.01	-2.74	Down
hsa-miR-634	0.07	0.01	-2.75	Down
hsa-miR-493-5p	0.07	0.01	-2.76	Down
hsa-miR-548c-3p	0.28	0.04	-2.78	Down
hsa-miR-585-3p	0.07	0.01	-2.80	Down
hsa-miR-211-5p	0.08	0.01	-2.92	Down
hsa-miR-328-3p	0.16	0.02	-2.93	Down
hsa-miR-515-3p	0.18	0.02	-3.03	Down
hsa-miR-372-3p	0.08	0.01	-3.04	Down
hsa-miR-338-3p	0.47	0.06	-3.04	Down
hsa-miR-9-3p	4.07	0.39	-3.37	Down
hsa-miR-380-3p	0.11	0.01	-3.40	Down
hsa-miR-371a-3p	0.12	0.01	-3.53	Down
hsa-miR-520h	0.12	0.01	-3.53	Down
hsa-miR-649	0.12	0.01	-3.63	Down
hsa-miR-326	0.52	0.04	-3.71	Down

hsa-miR-409-5p	0.14	0.01	-3.86	Down
hsa-miR-653-5p	0.16	0.01	-3.97	Down
hsa-miR-34c-5p	0.28	0.01	-4.80	Down
hsa-miR-124-3p	0.40	0.01	-5.33	Down
hsa-miR-146a-5p	6.50	0.10	-6.04	Down

RR, radioresistance; Pt, parental

Supplementary Table S3. List of enriched genes and miRNA in respective molecular pathways associated with radioresistance in HNC cells.

Functional modules	KEGG signaling pathway	miRNA (13)	Gene list (54 genes)
Cell motility	Focal adhesion	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-34c-5p, miR-380-3p, miR-409-5p, miR-499a-5p, miR-520a-3p, miR-520f-3p, miR-522-3p	GSK3B, JUN, ITGB4, ITGA3, LAMA3, LAMC1, THBS1, EGFR, IGF1R, VEGFA, FYN, PAK2, VCL
	Regulation of actin cytoskeleton	miR-199b-5p, miR-302b-3p, miR-34c-5p, miR-380-3p, miR-409-5p, miR-499a-5p, miR-520a-3p, miR-522-3p	NRAS, RRAS, ITGA3, ITGB4, RDX, MYH9, MYH10, PAK2, EGFR, VCL
	Adheres junction	miR-302b-3p, miR-34c-5p, miR-380-3p, miR-499a-5p, miR-522-3p	SMURF1, ARHGAP29, FYN, EGFR, VCL, IGF1R
	ECM-receptor interaction	miR-199b-5p, miR-380-3p, miR-409-5p	ITGA3, ITGB4, LAMA3, LAMC1, THBS1
RTK signaling	MAPK signaling pathway	miR-146a-5p, miR-199b-5p, miR-299-3p, miR-302b-3p, miR-34c-5p, miR-380-3p, miR-451a, miR-499a-5p, miR-517a-3p, miR-520a-3p, miR-520f-3p, miR-522-3p	JUN, IL1RAP, AREG, EGFR, IGF1R, VEGFA, IKBKB, PPP3CA, NRAS, DUSP10, RRAS, MYC, TRAF6, KIT, MKNK2, PAK2, MAP3K4
	ErbB signaling pathway	miR-199b-5p, miR-302b-3p, miR-380-3p, miR-451a, miR-499a-5p, miR-517a-3p, miR-520a-3p, miR-522-3p	GSK3B, CDKN1A, JUN, NRAS, MYC, AREG, PAK2, EGFR
	PI3K-Akt signaling pathway	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-380-3p, miR-409-5p, miR-451a, miR-499a-5p, miR-517a-3p, miR-520f-3p	GSK3B, CDKN1A, ITGB4, ITGA3, LAMA3, LAMC1, THBS1, AREG, EGFR, IGF1R, VEGFA, IKBKB, NRAS, PPP2R1B, MYC, KIT
	TGF-beta signaling pathway	miR-380-3p, miR-451a, miR-522-3p	PPP2R1B, SMURF1, MYC, FST, ID4, INHBA, THBS1
	EGFR TK inhibitor resistance	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-34c-5p, miR-380-3p	GSK3B, NRAS, AXL, EGFR, IGF1R, VEGFA
	Ras signaling pathway	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-34c-5p, miR-380-3p, miR-451a, miR-520a-3p, miR-520f-3p, miR-522-3p	BRAP, IKBKB, NRAS, RRAS, KIT, RASAL2, PAK2, EGFR, IGF1R, VEGFA
	Rap1 signaling pathway	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-34c-5p, miR-380-3p, miR-522-3p	NRAS, RRAS, KIT, GNAI3, THBS1, EGFR, IGF1R, VEGFA
Stress/Stemness	Wnt signaling pathway	miR-146a-5p, miR-199b-5p, miR-34c-5p, miR-451a, miR-499a-5p, miR-520f-3p, miR-522-3p	FZD1, FOSL1, VANGL1, GSK3B, PPP3CA, JUN, DAAM1, MYC, PSEN1
	p53 signaling pathway	miR-146a-5p, miR-199b-5p, miR-34c-5p, miR-380-3p, miR-499a-5p, miR-522-3p	CDKN1A, PERP, IGFBP3, SERPINE1, PMAIP1, THBS1
	Signaling pathway of PSCs	miR-146a-5p, miR-199b-5p, miR-34c-5p, miR-380-3p, miR-451a, miR-520f-3p, miR-522-3p	FZD1, GSK3B, NRAS, MYC, ID4, INHBA, KLF4, IGF1R
	Cellular senescence	miR-199b-5p, miR-34c-5p, miR-380-3p, miR-451a, miR-499a-5p, miR-520f-3p	PPP3CA, CDKN1A, NRAS, RRAS, MYC, IGFBP3, SERPINE1, ITPR3
	Notch signaling pathway	miR-199b-5p, miR-34c-5p, miR-520f-3p, miR-522-3p	NOTCH2, ADAM17, ATXN1, JAG1, PSEN1
	HIF-1 signaling pathway	miR-199b-5p, miR-299-3p, miR-302b-3p, miR-380-3p, miR-499a-5p, miR-520a-3p, miR-520f-3p	CDKN1A, MKNK2, SERPINE1, EGFR, IGF1R, VEGFA

Supplementary Table S4. List of antibodies used for Western blot analysis.

Antibody	Source	Cat. No.	Dilution
Anti-IGF1R	Abcam	ab182408	1:1000
Anti-p-ERK1/2 (Thr202/Tyr204)	Cell Signaling Technology	4370	1:1000
Anti-ERK1/2	Cell Signaling Technology	9102	1:1000
Anti-p-Akt (Ser473)	Abcam	ab81283	1:1000
Anti-Akt	Cell Signaling Technology	9272	1:1000
Anti-GAPDH	ABclonal	AC033	1:40000
Anti-MYH9	Abcam	ab138498	1:2000
Anti-GSK3 β	Cell Signaling Technology	9832	1:1000
Anti-VEGF	Santa Cruz	Sc-7269	1:500
Anti-mouse IgG, HRP-linked	Cell Signaling Technology	7076	1:5000
Anti-rabbit IgG, HRP-linked	Cell Signaling Technology	7074	1:5000

Catalog number (Cat.No.)