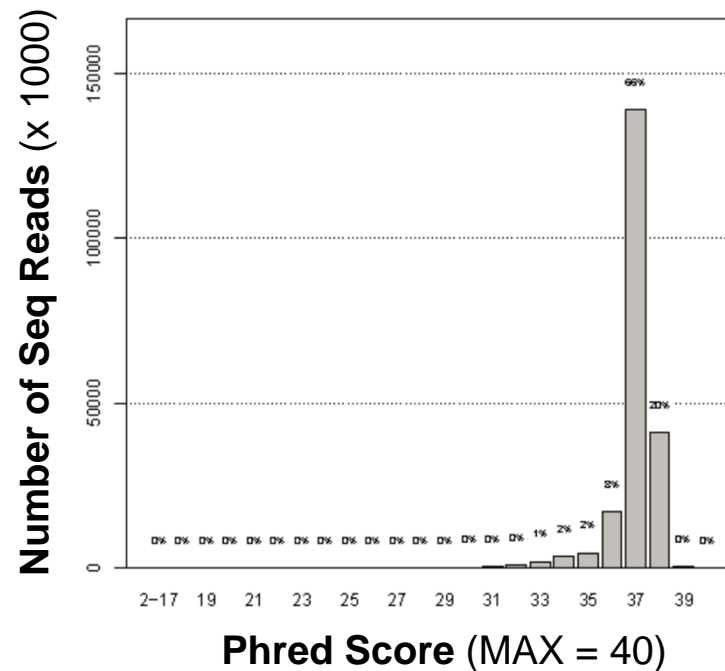
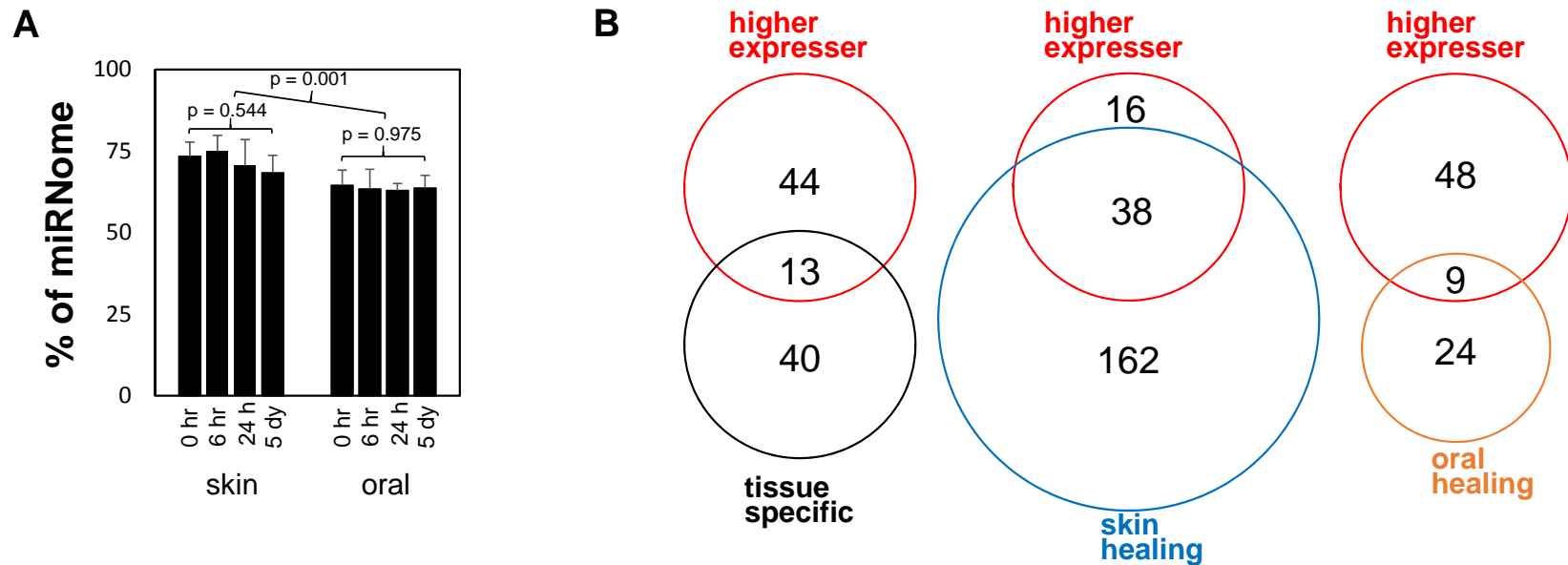


**Supplementary Figure S1: The highly expressed microRNAs account for major portion of the miRNome in oral and skin wounds, while the low expressing microRNAs dominant the percentage of unique mapped microRNA species.**

A previously reported miR-seq dataset on paired skin and oral mucosal wound healing [Sci. Rep. (2019) 9:7160] was used to examine the relationship of microRNA abundance and the number of unique microRNA species. The highly expressed microRNAs and the low expressing microRNAs are defined using the average number of mapped sequence reads of the overall miR-seq dataset (5458). **A**) The miRNome landscape was presented as histograms of percentage of mapped sequence reads vs. microRNAs grouped by their abundance (highly expressed microRNAs vs. low expressing microRNAs). **B**) The percentage of highly expressed microRNA species and low expressing microRNA species in skin and oral wounds were presented. **C**) Using a p value cut-off of 0.01, 53 are identified as tissue-specific differentially expressed microRNAs; 200 are differentially expressed in skin wound healing; 33 are differentially expressed in oral mucosal wound healing. The percentage of highly expressed microRNAs and low expressing microRNAs in each differentially expressed list is presented.

**Supplementary Figure S2: Relationship of sequencing accuracy and number of sequence reads.** Phred quality scores on the paired skin and oral mucosal wound healing miR-seq dataset were generated in real time during sequencing by Illumina platforms. A Histogram of the average phred score per base of mappable reads was presented. The phred score is the negative ratio of the error probability. Phred score larger than 30 stands for probability of incorrect base calls less than 1 in 1,000 (above 99.9% accuracy) in one sequencing read.

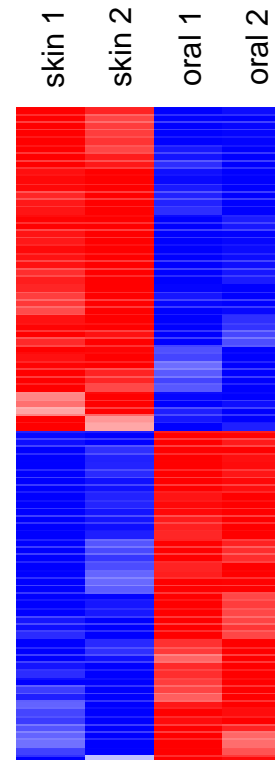




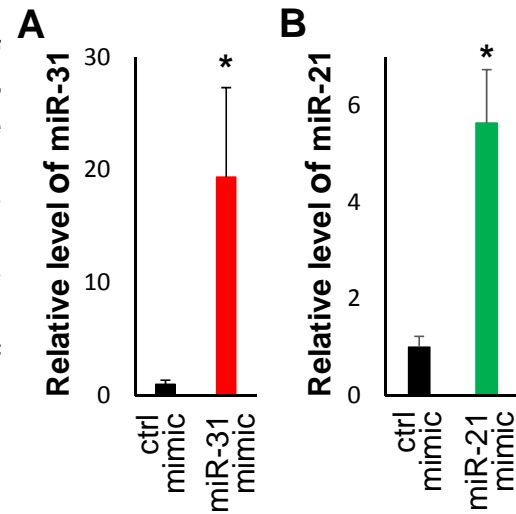
**Supplementary Figure S3: Characteristics of the 57 differentially expressed high expresser microRNAs.**

(A) The 57 differentially expressed high expresser microRNAs account for 73.4% and 64.5% of the miRNomes in skin and oral mucosa epithelium ( $p = 0.001$ ), and these fractions remaining relatively constant during the time course of the skin and oral mucosal wound healing ( $p=0.544$  and  $p=0.975$ , respectively). (B) Of the 57 differentially expressed high expresser microRNAs, 13 were previously identified as baseline tissue specific differentially expressed microRNAs, 38 were previously identified as differentially expressed microRNAs associated with skin wound healing, and 9 were previously identified as differentially expressed microRNAs associated with oral mucosal wound healing [Sci. Rep. (2019) 9:7160].

**Supplementary Figure S4: Tissue-specific differentially expressed microRNAs in skin and oral mucosal epithelium.** The microRNA profiling on matched mouse skin and oral mucosa samples (n=3, pooled) was performed using the MRA-1002 miRmouse v21 microarrays (LC Sciences, Houston, TX). Normalization and differential analysis were performed with CyberT. A panel of 85 tissue-specific differentially expressed microRNAs (q-value<0.01). List of the tissue-specific microRNAs was presented in Supplementary Table S2



**Supplementary Figure S5: Confirmation of the microRNA mimic mediated up-regulation of miR-31 and miR-21 in mouse skin wounds.** The miR-31 mimic, miR-21 mimic or negative control mimic were delivered to the mouse skin wounds using an animal origin-free lipid nanoparticle (Invivofectamine 3.0 Reagent from Invitrogen) at the time of injury. The microRNA mimic mediated up-regulation of miR-31 (**A**) and miR-21 (**B**) was confirmed by TaqMan assay-based real time PCR quantification on day 1 wound samples (\* p < 0.05).





**Supplementary Table S2: Tissue-specific differentially expressed microRNAs in mouse skin and oral mucosal epithelium**

<b>miR</b>	<b>fold (oral/skin)</b>	<b>corr. q-val</b>
mmu-miR-10b-5p	-1.982199442	3.55E-11
mmu-miR-451a	1.845365775	3.54E-10
mmu-miR-7211-3p	-1.743175942	5.49E-09
mmu-miR-10a-5p	-1.625557394	2.36E-08
mmu-miR-6540-5p	1.410432231	2.50E-08
mmu-miR-195a-3p	1.397298801	8.36E-08
mmu-miR-3103-5p	-1.374535577	2.82E-07
mmu-miR-665-5p	1.346613823	3.47E-07
mmu-miR-7082-5p	-1.196566429	5.24E-07
mmu-miR-6359	1.281108583	5.73E-07
mmu-miR-214-3p	1.269240053	1.01E-06
mmu-miR-7053-5p	1.352218936	1.13E-06
mmu-miR-6934-3p	1.325204188	1.35E-06
mmu-miR-678	-1.413271872	1.42E-06
mmu-miR-7647-3p	-1.342698653	1.63E-06
mmu-miR-7088-5p	-1.485014367	3.10E-06
mmu-miR-16-1-3p	1.337582778	3.60E-06
mmu-miR-7045-5p	-1.163735769	5.56E-06
mmu-miR-7082-3p	1.29298308	6.54E-06
mmu-miR-5104	-1.31362353	8.28E-06
mmu-miR-3473d	1.222056189	9.41E-06
mmu-miR-34b-3p	1.215255043	9.74E-06
mmu-miR-29c-5p	-1.483350303	1.24E-05
mmu-miR-150-5p	1.332006747	1.75E-05
mmu-miR-7022-3p	1.338666348	2.35E-05
mmu-miR-7075-5p	-1.446507597	2.37E-05
mmu-miR-676-3p	-1.199742321	3.65E-05
mmu-miR-7052-5p	-1.246722765	3.76E-05
mmu-miR-346-5p	1.430519097	4.41E-05
mmu-miR-146b-5p	-1.281482583	5.20E-05
mmu-miR-196a-5p	-1.284334608	5.54E-05
mmu-miR-101a-3p	-1.218546765	8.62E-05
mmu-miR-3070b-3p	-1.266188851	8.69E-05
mmu-miR-6942-5p	-1.348172231	0.000124
mmu-miR-1907	-1.421860348	0.000134
mmu-miR-705	-1.139990737	0.000137
mmu-miR-15a-3p	1.33767164	0.000196
mmu-miR-126a-3p	1.241031615	0.000212
mmu-miR-5112	-1.221503256	0.000223
mmu-miR-6931-5p	-1.177801676	0.000303
mmu-miR-6360	1.255440277	0.0004
mmu-miR-3473e	1.172623409	0.000427
mmu-miR-1983	1.176768986	0.000476
mmu-miR-467a-5p	1.165063814	0.000629
mmu-miR-374c-5p	-1.211108401	0.000634

mmu-miR-7235-5p	-1.3195672	0.000667
mmu-miR-375-3p	1.210377267	0.000668
mmu-miR-199a-3p	1.173644383	0.000686
mmu-miR-31-5p	1.146336437	0.000772
mmu-miR-365-3p	-1.230574533	0.000802
mmu-miR-138-2-3p	1.150686421	0.000809
mmu-let-7f-5p	-1.104261244	0.000827
mmu-miR-207	1.172299327	0.000877
mmu-miR-6980-5p	-1.177513002	0.001088
mmu-miR-1903	1.142199127	0.00113
mmu-miR-7665-5p	1.196517681	0.001178
mmu-miR-7028-5p	-1.205054435	0.00124
mmu-let-7k	-1.220767225	0.001302
mmu-miR-200c-3p	-1.090876142	0.001477
mmu-miR-6952-3p	1.141600262	0.001813
mmu-miR-3098-3p	1.157332636	0.001904
mmu-miR-7048-5p	-1.165290162	0.002081
mmu-miR-6996-5p	1.266197036	0.00211
mmu-miR-6958-3p	1.214933705	0.002136
mmu-miR-690	-1.076752067	0.002158
mmu-miR-7033-5p	-1.147956187	0.002453
mmu-miR-3569-3p	1.15329023	0.00252
mmu-miR-7578	1.267530421	0.002837
mmu-miR-3107-5p	1.158352835	0.002958
mmu-miR-466p-5p	-1.195193276	0.003021
mmu-miR-1187	1.083117192	0.003603
mmu-miR-6929-3p	1.138323233	0.003694
mmu-miR-6368	-1.142107201	0.003779
mmu-miR-181d-5p	1.20708225	0.003878
mmu-miR-7080-5p	-1.196021925	0.00391
mmu-miR-15b-5p	-1.12129573	0.004122
mmu-miR-6939-5p	-1.175468921	0.004307
mmu-miR-98-5p	-1.165509765	0.004612
mmu-miR-7049-3p	1.237488124	0.005555
mmu-miR-214-5p	1.23282749	0.006668
mmu-miR-7034-5p	1.140768613	0.006939
mmu-let-7a-5p	-1.066357154	0.007239
mmu-miR-7211-5p	1.155266855	0.008024
mmu-miR-7225-3p	1.122008402	0.008558
mmu-miR-744-5p	-1.211651849	0.009022

MicroRNA expression was measured using a mouse MicroRNA Microarray (LC Sciences) on pooled RNA samples isolated from mouse skin and oral mucosa samples (n=3). Differential expression analysis was performed with CyberT using a VSN normalization procedure.

Multiple hypothesis testing correction is performed with Bonferroni procedure, and Bonferroni corrected q-values were presented.

Cut-off q-value of 0.01 was used.



**Supplementary Table S3: Validation of the tissue specificity of 57 differentially expressed high expresser microRNAs with independent miR profiling experiments**

Index	Reporter Name	cluster *	Original Dataset **	Validation Dataset***
			tissue specific	tissue specific
80	mmu-miR-10a-5p	I	1	1
1	rno-miR-378a-3p	I	1	x
38	mmu-miR-223-3p	I	1	no match
65	mmu-miR-146b-5p	I	1	1
73	mmu-miR-133a-3p	I	1	x
48	mmu-miR-1a-3p	I	1	x
42	mmu-miR-206-3p	I	x	x
79	mmu-miR-10b-5p	I	1	1
11	mmu-miR-541-5p	I	x	no match
72	mmu-miR-133b-3p	I	x	x
17	mmu-miR-434-5p	I	x	no match
74	mmu-miR-127-3p	I	x	no match
82	mmu-let-7j	I	x	x
70	mmu-miR-142a-5p	I	x	no match
41	mmu-miR-21a-5p	II	x	x
63	mmu-miR-148b-3p	II	x	x
2	rno-miR-25-3p	II	x	x
83	mmu-let-7g-5p	II	x	x
5	ptr-let-7i	II	x	x
3	rno-miR-140-3p	II	x	x
12	mmu-miR-5099	II	x	x
58	mmu-miR-15b-5p	II	x	1
59	mmu-miR-152-3p	II	x	x
28	mmu-miR-30a-5p	III	1	x
51	mmu-miR-195a-5p	III	x	x
25	mmu-miR-30d-5p	III	x	x
33	mmu-miR-26a-5p	III	x	x
8	mmu-miR-96-5p	III	1	no match
7	mmu-miR-99a-5p	III	x	x
67	mmu-miR-145a-5p	III	x	x
47	mmu-miR-200a-3p	III	x	x
34	mmu-miR-24-3p	III	x	x
69	mmu-miR-143-3p	III	x	x
84	mmu-let-7f-5p	III	x	1
53	mmu-miR-186-5p	III	x	x
23	mmu-miR-31-5p	IV	1	1
50	mmu-miR-199a-5p	IV	x	x
76	mmu-miR-126a-3p	IV	x	1
21	mmu-miR-34c-5p	IV	1	no match
16	mmu-miR-451a	IV	1	1
49	mmu-miR-199b-3p	IV	x	1
75	mmu-miR-126a-5p	IV	1	no match
35	mmu-miR-24-2-5p	IV	x	x
36	mmu-miR-23b-3p	V	x	x
44	mmu-miR-203-3p	V	x	x
46	mmu-miR-200b-3p	V	x	x
77	mmu-miR-125b-5p	V	x	x
45	mmu-miR-200c-3p	V	x	1
30	mmu-miR-27b-3p	V	x	x
56	mmu-miR-181a-5p	V	x	x
78	mmu-miR-125a-5p	V	x	x
55	mmu-miR-182-5p	V	x	x
68	mmu-miR-145a-3p	V	x	no match
37	mmu-miR-23a-3p	V	x	x
43	mmu-miR-205-5p	V	x	x
54	mmu-miR-183-5p	V	x	x
88	mmu-let-7b-5p	V	x	x

miRNAs shown significant difference ( $p < 0.01$ ), and have the number of reads  $>$  the average (5458) of the dataset.

\*: clusters were defined based on Hierarchical Clustering analysis using Morpheus.

\*\*: Original dataset:Tissue-specific differential expressed miRs were defined in [Sci. Rep. (2019) 9:7160].

\*\*\*: Validation dataset 1: Tissue-specific differential expressed miRs were identified by microarray analysis using paired skin and oral mucosal tissue samples from mice.

**Supplementary Table S4: Statistical analysis on differential expression of selected microRNAs**

**Cluster I**

**mmu-miR-10b-5p**

**miR-Seq**

hour	skin	oral	stdev (s)	stdev (o)
0	1	0.16388	0.15904	0.0479
6	0.92243	0.15016	0.40317	0.04879
24	0.30263	0.14704	0.09113	0.03919
120	0.20605	0.1517	0.06824	0.02766

one-way ANOVA (skin) **p-value = 0.0042662840**  
 one-way ANOVA (oral) p-value = 0.9613844771

two-way ANOVA **p-value = 3.514122e-6**

**LCM/TaqMan**

hour	skin	oral	stdev (s)	stdev (o)
0	1.05813	0.05347	0.4068	0.01685
6	1.33081	0.03662	0.48886	0.02027
24	0.42458	0.08254	0.31821	0.08102
120	0.27895	0.04671	0.18151	0.0611

one-way ANOVA (skin) **p-value = 0.0000004779**  
 one-way ANOVA (oral) p-value = 0.4325128555

two-way ANOVA **p-value = 1.951684e-8**

**mmu-miR-223-3p**

**miR-Seq**

hour	skin	oral	stdev (s)	stdev (o)
0	0.999953	0.408908	0.189619	0.033747
6	3.472382	1.087826	1.045229	0.353727
24	21.88087	1.522174	7.092387	1.005989
120	5.341474	0.439913	2.798091	0.07146

one-way ANOVA (skin) **p-value = 0.0006251456**  
 one-way ANOVA (oral) p-value = 0.0924204518

two-way ANOVA **p-value = 1.071586e-5**

**LCM/TaqMan**

hour	skin	oral	stdev (s)	stdev (o)
0	1.00479	0.22033	0.1055	0.1498
6	6.96063	4.32524	3.43335	2.17314
24	90.333	0.82264	22.3316	0.14561
120	71.283	0.46588	36.6742	0.11096

one-way ANOVA (skin) **p-value = 0.0005539250**  
 one-way ANOVA (oral) **p-value = 0.0000051701**

two-way ANOVA **p-value = 1.393415e-6**

**Cluster II**

**mmu-miR-21-5p**

**miR-Seq**

hour	skin	oral	stdev (s)	stdev (o)
0	1.000012	0.962027	0.253921	0.212693
6	1.99411	1.932654	0.280097	1.395369
24	4.56857	3.380248	0.344211	0.651479
120	8.705052	3.00985	1.466047	0.855424

one-way ANOVA (skin) **p-value = 0.0000085387**  
 one-way ANOVA (oral) **p-value = 0.0381469755**

two-way ANOVA **p-value = 1.008347e-4**

**LCM/TaqMan**

hour	skin	oral	stdev (s)	stdev (o)
0	1.1171	0.31085	0.54907	0.2744
6	0.94479	0.13192	0.34645	0.07162
24	1.61073	1.26236	0.47516	1.3955
120	4.80132	1.32614	2.10515	0.79613

one-way ANOVA (skin) **p-value = 0.0000000000**  
 one-way ANOVA (oral) **p-value = 0.0070474133**

two-way ANOVA **p-value = 0.000000e+0**

**mmu-miR-140-3p**

**miR-Seq**

hour	skin	oral	stdev (s)	stdev (o)
0	1.000043	2.391934	0.032481	0.996564
6	0.816283	2.034733	0.129787	0.363597
24	2.936411	2.40483	0.404628	1.364335
120	1.611947	2.471958	0.037683	0.4306

one-way ANOVA (skin) **p-value = 0.0000077748**  
 one-way ANOVA (oral) p-value = 0.9286297066

two-way ANOVA **p-value = 0.01341338**

**LCM/TaqMan**

hour	skin	oral	stdev (s)	stdev (o)
0	1	0.37114	0.93355	0.3016
6	3.7718	1.27243	2.34304	0.46806
24	6.80201	0.48988	5.23345	0.22643
120	5.65733	1.41787	4.49115	0.31332

one-way ANOVA (skin) **p-value = 0.0024882129**  
 one-way ANOVA (oral) **p-value = 0.0000007733**

two-way ANOVA **p-value = 8.485368e-11**

**Cluster III**

**mmu-miR-99a-5p**

**miR-Seq**

hour	skin	oral	stdev (s)	stdev (o)
0	1	1.140749	0.0842	0.178556
6	1.5238	1.386114	0.182855	0.348079
24	0.873889	1.039303	0.208621	0.085498
120	0.537912	1.013975	0.148197	0.049289

one-way ANOVA (skin) **p-value = 0.0005390556**  
 one-way ANOVA (oral) p-value = 0.1752214836

**LCM/TaqMan**

hour	skin	oral	stdev (s)	stdev (o)
0	1.03602	2.7167	0.28881	1.63517
6	3.26437	2.85863	1.77585	1.516
24	0.9841	1.10762	0.39102	0.34286
120	1.14221	1.47977	0.1581	0.40894

one-way ANOVA (skin) **p-value = 0.0168764875**  
 one-way ANOVA (oral) p-value = 0.1988154933

two-way ANOVA p-value = 4.689403e-2

two-way ANOVA p-value = 1.579563e-1

**mmu-miR-26a-5p**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
hour	0	1	0.75499	0.225197
	6	0.854867	0.777713	0.115354
	24	0.482248	0.647254	0.036568
	120	0.403676	0.58426	0.056791

one-way ANOVA (skin) p-value = 0.0013458458

one-way ANOVA (oral) p-value = 0.1059181021

two-way ANOVA p-value = 9.013084e-1

**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.00351	0.70583	0.09241
	6	1.40049	0.49348	0.21375
	24	0.21055	0.1531	0.1158
	120	0.47231	0.63376	0.14798

one-way ANOVA (skin) p-value = 0.0000000000

one-way ANOVA (oral) p-value = 0.0000000001

two-way ANOVA p-value = 5.532423e-10

**Cluster IV**

**mmu-miR-31-5p**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
hour	0	0.999445	22.83856	0.32007
	6	0.668761	18.30634	0.422295
	24	0.840345	21.58825	0.388254
	120	11.68245	33.95408	1.796909

one-way ANOVA (skin) p-value = 0.0000012741

one-way ANOVA (oral) p-value = 0.0013593949

two-way ANOVA p-value = 2.132738e-13

**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.03405	6.83589	0.27175
	6	0.45834	10.0726	0.21271
	24	0.20257	8.63327	0.05702
	120	17.5665	46.2521	4.16547

one-way ANOVA (skin) p-value = 0.0000000001

one-way ANOVA (oral) p-value = 0.0000422971

two-way ANOVA p-value = 1.503829e-5

**mmu-miR-451a**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.000601	20.20339	0.302476
	6	3.568201	12.31014	0.832018
	24	4.648233	20.71412	1.287771
	120	6.477267	9.422348	6.510191

one-way ANOVA (skin) p-value = 0.3112343244

one-way ANOVA (oral) p-value = 0.5880771974

two-way ANOVA p-value = 4.604120e-3

**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
hour	0	1	8.52394	0.52108
	6	75.7683	39.9092	59.1761
	24	42.3235	101.572	53.6771
	120	67.436	240.362	73.0032

one-way ANOVA (skin) p-value = 0.0495521565

one-way ANOVA (oral) p-value = 0.0000203422

two-way ANOVA p-value = 1.102023e-1

**mmu-miR-34c-5p**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.0029	83.8442	0.35551
	6	1.89588	156.927	0.31428
	24	3.45167	65.0702	0.59518
	120	35.32	47.1006	30.0751

one-way ANOVA (skin) p-value = 0.0628504365

one-way ANOVA (oral) p-value = 0.5435316838

two-way ANOVA p-value = 1.296908e-2

**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.17721	64.2194	0.74403
	6	1.5443	82.8872	0.4456
	24	2.96769	35.3505	1.53904
	120	14.4752	162.254	2.07662

one-way ANOVA (skin) p-value = 0.0000000000

one-way ANOVA (oral) p-value = 0.0022578420

two-way ANOVA p-value = 1.307810e-9

**mmu-miR-24-2-5p**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.00001	0.85222	0.04154
	6	0.73267	0.80686	0.05773
	24	0.51965	0.91515	0.12041
	120	0.73675	0.83981	0.07881

one-way ANOVA (skin) p-value = 0.0006448633

one-way ANOVA (oral) p-value = 0.8934766793

two-way ANOVA p-value = 7.469976e-2

**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
hour	0	1.02554	0.68663	0.24149
	6	0.82815	0.64816	0.05124
	24	0.71884	0.4451	0.20117
	120	0.53665	0.80411	0.0627

one-way ANOVA (skin) p-value = 0.0004074361

one-way ANOVA (oral) p-value = 0.0378170837

two-way ANOVA p-value = 1.629529e-2

**mmu-miR-126a-5p**

**miR-Seq**

	skin	oral	stdev (s)	stdev (o)
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**LCM/TaqMan**

	skin	oral	stdev (s)	stdev (o)
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hour	0	0.9999	1.86429	0.14287	0.28658
	6	1.53863	2.16924	0.27783	0.51213
	24	0.93591	1.86845	0.32264	0.72061
	120	1.54199	1.34584	0.28748	0.2903

one-way ANOVA (skin) [p-value = 0.0367424477](#)  
 one-way ANOVA (oral) [p-value = 0.2915927220](#)

two-way ANOVA [p-value = 3.080962e-3](#)

#### mmu-miR-126a-3p

##### miR-Seq

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.00002	1.19993	0.02154	0.07708
	6	0.95078	1.28321	0.14976	0.14097
	24	0.71712	1.11503	0.08872	0.11381
	120	1.03943	1.23769	0.05516	0.10387

one-way ANOVA (skin) [p-value = 0.0107302984](#)  
 one-way ANOVA (oral) [p-value = 0.3604404602](#)

two-way ANOVA [p-value = 4.500348e-6](#)

#### mmu-miR-199a-5p

##### miR-Seq

	skin	oral	stdev (s)	stdev (o)	
hour	0	1	1.28941	0.05623	0.13984
	6	0.74372	1.38509	0.14003	0.15188
	24	0.49441	1.13167	0.11297	0.10105
	120	1.25567	1.28514	0.26768	0.15811

one-way ANOVA (skin) [p-value = 0.0024600154](#)  
 one-way ANOVA (oral) [p-value = 0.2449372673](#)

two-way ANOVA [p-value = 8.279114e-6](#)

#### mmu-miR-199b-3p

##### miR-Seq

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.00002	1.61231	0.29356	0.11655
	6	1.33978	2.08999	0.2308	0.05308
	24	1.21826	1.78838	0.12986	0.50673
	120	1.74177	2.02731	0.13536	0.14602

one-way ANOVA (skin) [p-value = 0.0144157380](#)  
 one-way ANOVA (oral) [p-value = 0.1954840301](#)

two-way ANOVA [p-value = 3.915706e-5](#)

### Cluster V

#### mmu-miR-125b-5p

##### miR-Seq

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.000001	1.138808	0.261571	0.157288
	6	0.602217	0.948907	0.100906	0.23488
	24	0.316224	0.641391	0.035158	0.100507
	120	0.494231	0.738349	0.075924	0.139347

one-way ANOVA (skin) [p-value = 0.0026510959](#)  
 one-way ANOVA (oral) [p-value = 0.0250541501](#)

two-way ANOVA [p-value = 7.743095e-4](#)

#### mmu-miR-125a-5p

##### miR-Seq

	skin	oral	stdev (s)	stdev (o)	
hour	0	0.999995	0.784881	0.337814	0.103334
	6	0.521206	0.677937	0.104037	0.236693
	24	0.290362	0.360574	0.031068	0.091706
	120	0.470782	0.596849	0.091684	0.145685

one-way ANOVA (skin) [p-value = 0.0080004410](#)

hour	0	1.02281	1.13154	0.23304	0.61011
	6	0.82478	0.74533	0.21692	0.09552
	24	0.60181	0.50036	0.18889	0.26269
	120	0.75244	0.90493	0.17029	0.13916

one-way ANOVA (skin) [p-value = 0.0153397840](#)  
 one-way ANOVA (oral) [p-value = 0.0311976849](#)

two-way ANOVA [p-value = 8.064029e-1](#)

##### LCM/TaqMan

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.0121	1.08732	0.17104	0.33538
	6	1.07103	1.06201	0.26453	0.1185
	24	0.75819	0.59221	0.07656	0.19267
	120	0.84919	0.99827	0.04835	0.3132

one-way ANOVA (skin) [p-value = 0.0126603858](#)  
 one-way ANOVA (oral) [p-value = 0.0101819129](#)

two-way ANOVA [p-value = 8.434429e-1](#)

##### LCM/TaqMan

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.03981	1.66483	0.31694	0.80451
	6	1.0016	1.03396	0.1058	0.22706
	24	0.78837	0.58865	0.12739	0.10116
	120	1.40373	1.11833	0.51087	0.25234

one-way ANOVA (skin) [p-value = 0.0215631834](#)  
 one-way ANOVA (oral) [p-value = 0.0041670237](#)

two-way ANOVA [p-value = 6.975289e-1](#)

##### LCM/TaqMan

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.00866	1.53192	0.14737	0.42251
	6	0.93754	0.90036	0.20295	0.09239
	24	1.03203	0.60616	0.17864	0.18131
	120	0.92642	0.87223	0.11186	0.05888

one-way ANOVA (skin) [p-value = 0.6181493984](#)  
 one-way ANOVA (oral) [p-value = 0.0000120929](#)

two-way ANOVA [p-value = 9.796490e-1](#)

##### LCM/TaqMan

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.0807	1.81417	0.38263	0.6528
	6	1.09994	0.33573	0.31694	0.13976
	24	0.27759	0.74107	0.27759	0.37983
	120	1.04861	0.86166	0.40312	0.42776

one-way ANOVA (skin) [p-value = 0.0000006328](#)  
 one-way ANOVA (oral) [p-value = 0.0000533232](#)

two-way ANOVA [p-value = 3.550410e-1](#)

##### LCM/TaqMan

	skin	oral	stdev (s)	stdev (o)	
hour	0	1.13827	0.73804	0.50428	0.18046
	6	1.96972	1.24938	1.08421	0.37058
	24	0.19846	0.13364	0.13421	0.06417
	120	1.39059	0.99888	0.90191	0.10161

one-way ANOVA (skin) [p-value = 0.0034683330](#)

one-way ANOVA (oral) p-value = 0.0505159562

two-way ANOVA p-value = 6.257289e-1

one-way ANOVA (oral) p-value = 0.0000341469

two-way ANOVA p-value = 1.078114e-3

**Supplementary Table S5: Statistical analysis on wound closure**

**A: in vitro wounds treated with control and miR-21 mimic**

**A.1: 2way ANOVA - in vitro wounds treated with control and miR-21 mimic**

Two-way ANOVA		Ordinary					Significant?
Alpha		0.05					
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value		
Interaction	688	3	229.3	F (3, 18) = 3.006	P = 0.0575	No	
Row Factor (time)	12361	3	4120	F (3, 18) = 54.01	P < 0.0001	Yes	
Column Factor (treatment)	6790	1	6790	F (1, 18) = 89.00	P < 0.0001	Yes	
Residual	1373	18	76.29				

**A.2: Bonferroni's multiple comparisons test - in vitro wounds treated with control and miR-21 mimic**

		Mean (ctrl)	Mean (miR-21)	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
day 1	Row 1	15.49	32.27	-16.78	-35.29 to 1.727	No	ns	0.0864
day 2	Row 2	17.44	64.13	-46.69	-68.81 to -24.57	Yes	****	< 0.0001
day 3	Row 3	53.88	90.14	-36.26	-54.77 to -17.75	Yes	***	0.0001
day 4	Row 4	58.83	91.54	-32.71	-51.21 to -14.20	Yes	***	0.0005

**B: in vitro wounds treated with control and miR-31 mimic**

**B.1: 2way ANOVA - in vitro wounds treated with control and miR-31 mimic**

Two-way ANOVA		Ordinary					Significant?
Alpha		0.05					
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value		
Interaction	1579	3	526.3	F (3, 22) = 10.79	P = 0.0001	Yes	
Row Factor (time)	12314	3	4105	F (3, 22) = 84.16	P < 0.0001	Yes	
Column Factor (treatment)	16346	1	16346	F (1, 22) = 335.2	P < 0.0001	Yes	
Residual	1073	22	48.77				

**B.2: Bonferroni's multiple comparisons test - in vitro wounds treated with control and miR-31 mimic**

		Mean (ctrl)	Mean (miR-31)	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
day 1	Row 1	15.49	45.93	-30.44	-43.87 to -17.01	Yes	****	< 0.0001
day 2	Row 2	17.44	91.49	-74.05	-90.50 to -57.60	Yes	****	< 0.0001
day 3	Row 3	53.88	100	-46.12	-59.55 to -32.69	Yes	****	< 0.0001
day 4	Row 4	58.83	100	-41.17	-54.60 to -27.73	Yes	****	< 0.0001

**C: in vivo murine skin wounds treated with control and miR-21 mimic**

**C.1: 2way ANOVA - in vivo murine skin wounds treated with control and miR-21 mimic**

Two-way ANOVA		Ordinary					Significant?
Alpha		0.05					
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value		
Interaction	137.4	9	15.27	F (9, 90) = 0.3972	P = 0.9335	No	
Row Factor (time)	78932	9	8770	F (9, 90) = 228.1	P < 0.0001	Yes	
Column Factor (treatment)	259.5	1	259.5	F (1, 90) = 6.751	P = 0.0109	Yes	
Residual	3460	90	38.44				

**C.2: Bonferroni's multiple comparisons test - in vivo murine skin wounds treated with control and miR-21 mimic**

		Mean (ctrl)	Mean (miR-21)	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
day 1	Row 1	15.91	18.62	-2.708	-13.51 to 8.097	No	ns	> 0.9999
day 2	Row 2	27.35	33.92	-6.57	-17.37 to 4.235	No	ns	0.8354
day 3	Row 3	40.3	40.68	-0.3766	-11.18 to 10.43	No	ns	> 0.9999
day 4	Row 4	51.2	52.35	-1.146	-11.95 to 9.659	No	ns	> 0.9999
day 5	Row 5	58.17	61.45	-3.28	-14.08 to 7.525	No	ns	> 0.9999
day 6	Row 6	61.85	68.09	-6.237	-17.04 to 4.567	No	ns	> 0.9999
day 7	Row 7	70.57	76.67	-6.107	-16.91 to 4.698	No	ns	> 0.9999
day 8	Row 8	92.89	94.15	-1.26	-12.06 to 9.545	No	ns	> 0.9999
day 9	Row 9	96.26	97.7	-1.432	-12.24 to 9.373	No	ns	> 0.9999
day 10	Row 10	97.51	99.25	-1.732	-12.54 to 9.073	No	ns	> 0.9999

**D: in vivo murine skin wounds treated with control and miR-31 mimic**

**D.1: 2way ANOVA - in vivo murine skin wounds treated with control and miR-31 mimic**

Two-way ANOVA		Ordinary					Significant?
Alpha		0.05					
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value		
Interaction	2000	9	222.2	F (9, 100) = 5.096	P < 0.0001	Yes	
Row Factor (time)	66462	9	7385	F (9, 100) = 169.4	P < 0.0001	Yes	
Column Factor (treatment)	4887	1	4887	F (1, 100) = 112.1	P < 0.0001	Yes	
Residual	4360	100	43.6				

**D.2: Bonferroni's multiple comparisons test - in vivo murine skin wounds treated with control and miR-31 mimic**

		Mean (ctrl)	Mean (miR-31)	Mean Diff.	95% CI of diff.	Significant?	Summary	Adjusted P Value
day 1	Row 1	15.91	34.05	-18.14	-29.08 to -7.194	Yes	****	< 0.0001
day 2	Row 2	27.35	54.9	-27.54	-38.48 to -16.60	Yes	****	< 0.0001
day 3	Row 3	40.3	63.57	-23.26	-34.21 to -12.32	Yes	****	< 0.0001
day 4	Row 4	51.2	65.9	-14.7	-25.64 to -3.753	Yes	**	0.002
day 5	Row 5	58.17	68.4	-10.23	-21.18 to 0.7104	No	ns	0.0851
day 6	Row 6	61.85	75.37	-13.52	-24.46 to -2.574	Yes	**	0.006
day 7	Row 7	70.57	82.33	-11.77	-22.71 to -0.8251	Yes	*	0.0262
day 8	Row 8	92.89	96.39	-3.495	-14.44 to 7.449	No	ns	> 0.9999
day 9	Row 9	96.26	99.05	-2.787	-13.73 to 8.157	No	ns	> 0.9999
day 10	Row 10	97.51	99.7	-2.187	-13.13 to 8.757	No	ns	> 0.9999

## Supplementary Table S6a: Bioinformatics prediction of pathways targeted by mmu-miR-31-3p

KEGG pathway	p-value	#genes targeted	gene targeted
Steroid biosynthesis	1.22E-08	1	Dhcr24
Steroid hormone biosynthesis	4.39E-07	1	Hsd3b1
Vitamin B6 metabolism	0.00946592	1	Sh3bp1
Thiamine metabolism	0.00948411	1	Tpk1
Adrenergic signaling in cardiomyocyte	0.00948411	3	Ppp2r2a, Cacnb2, Ppp2r3c
Sphingolipid metabolism	0.02507051	2	Sgpp2, B4galt6
B cell receptor signaling pathway	0.02624945	3	Vav3, Cd72, Ppp3ca
MAPK signaling pathway	0.03228995	6	Mef2c, Map3k1, Cacnb2, Dusp7, Rasa1, Ppp3ca
Taurine and hypotaurine metabolism	0.04608911	1	Gad2
Gap junction	0.04672907	1	Gjd2
Ovarian steroidogenesis	0.04672907	1	Hsd3b1
mRNA surveillance pathway	0.04845908	4	Ppp2r2a, Cpsf2, Ppp2r3c, Nxf1
Axon guidance	0.04845908	4	Rasa1, Ppp3ca, EphA7, Sema6c

MicroRNA targeted pathway analysis were performed using DIANA-mirPath (v3.0), with microT-CDS as microRNA target prediction method (microT threshold = 0.8). A cut off p value of 0.05 was used.

## Supplementary Table S6b: Bioinformatics prediction of pathways targeted by Cluster IV microRNAs

KEGG pathway	p-value	#microRNAs	#genes targeted	microRNA	gene
Steroid hormone biosynthesis	7.68E-20	3	10	mmu-miR-126a-5p mmu-miR-31-5p mmu-miR-34c-5p	Ugt1a6b, Ugt1a2, Ugt1a9, Ugt1a10, Ugt1a7c, Ugt1a5, Ugt1a1, Ugt1a6; Hsd3b1 Cyp2c54
Drug metabolism - cytochrome P450	5.25E-05	1	8	mmu-miR-126a-5p	Ugt1a6b, Ugt1a2, Ugt1a9, Ugt1a10, Ugt1a7c, Ugt1a5, Ugt1a1, Ugt1a6;
Dorso-ventral axis formation	0.00010201	5	10	mmu-miR-34c-5p mmu-miR-24-2-5p mmu-miR-199b-3p mmu-miR-126a-5p mmu-miR-199a-5p	Notch1, Map2k1, Notch2, Notch4 Kras Cpeb3 Cpeb2, Sos1 Sos2, Ets1
Gap junction	0.00062218	6	9	mmu-miR-34c-5p mmu-miR-126a-5p mmu-miR-199b-3p mmu-miR-31-5p mmu-miR-199a-5p mmu-miR-24-2-5p	Map2k1, Grm1 Sos1, Map3k2 Plcb1, Gja1 Gjd2 Sos2 Kras
Proteoglycans in cancer	0.00062218	6	23	mmu-miR-34c-5p mmu-miR-199a-5p mmu-miR-126a-5p mmu-miR-199b-3p mmu-miR-24-2-5p mmu-miR-31-5p	Map2k1, Camk2b, Araf, Met, Rras Tgfb2, Sos2, Wnt7b, Fzd10, Fzd4, Fzd5 ErbB4, Wnt16, Ank3, Sos1, Cd44 Cblb, Igf1, ErbB4, Arhgef12, Fn1, Met, Mtor Kras Fzd3
AMPK signaling pathway	0.00381211	7	18	mmu-miR-34c-5p mmu-miR-24-2-5p mmu-miR-199a-5p mmu-miR-199b-3p mmu-miR-31-5p	Irs4, Ppp2r3a, Creb1, Ppp2r5e Ppp2r5c Rab10, Slc2a4, Stradb, Prkag2, Sirt1 Scd2, Ppp2r2a, Igf1, Scd4, Mtor Ppp2r2a, Ppp2r3c, Sirt1

				mmu-miR-126a-5p mmu-miR-126a-3p	Ppargc1a Irs1
Wnt signaling pathway	0.00682663	5	16	mmu-miR-31-5p mmu-miR-126a-5p mmu-miR-199b-3p mmu-miR-199a-5p mmu-miR-34c-5p	Fzd3, Ppp3ca Axin1, Wnt16, Cxxc4, Ppp3ca Csnk1a1, Plcb1, Mapk8 Wnt7b, Gsk3b, Fzd10, Fzd4, Fzd5 Lef1, Camk2b, Daam1
Ascorbate and aldarate metabolism	0.00721958	1	8	mmu-miR-126a-5p	Ugt1a6b, Ugt1a2, Ugt1a9, Ugt1a10, Ugt1a7c, Ugt1a5, Ugt1a1, Ugt1a6:

MicroRNA targeted pathway analysis were performed using DIANA-mirPath (v3.0), with microT-CDS as microRNA target prediction method (microT threshold = 0.8). A cut off p value of 0.01 was used.