

# Oral spirochete *Treponema denticola* intraoral infection reveals unique miR-133a, miR-486, miR-126-3p, miR-126-5p miRNA expression kinetics during periodontitis.

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## Supplemental information

**Table S1.** Downregulated miRNAs during 8-weeks of infection, molecular functions, and target genes.

miRNAs	Fold change	p-value	Reported functions	Number of Target Genes
miR-375	-2.02	0.0421	Down regulated in oral squamous cell carcinoma [1]. Salivary adenoid cystic carcinoma had downregulated miR-375 [2].	276 ( <i>Bmpr2</i> , <i>Mtpn</i> , <i>Klf4</i> , <i>Enah</i> , <i>Fzd8</i> , <i>F10</i> , <i>Zfpn2</i> , <i>Atxn7</i> , <i>Rs1</i> , <i>Tsc1</i> , <i>Pdpk1</i> , <i>Uvssa</i> , <i>Nufip2</i> )
miR-34b-5p	-1.73	0.0357	Enhance the resistance to bleomycin by regulating its target gene TIMP3 during the pathogenesis of lung fibrosis [3].	355 ( <i>Arhgap1</i> , <i>Ppp4r2</i> , <i>Dixdc1</i> , <i>Htr2c</i> , <i>Rpap1</i> , <i>N4bp1</i> , <i>Tbc1d2b</i> , <i>Rab3c</i> )
miR-210	-1.55	0.0095	Induces endothelial dysfunction in type 2 diabetes. Promoting regulatory T-cell signaling in periodontitis [4].	16 ( <i>Onecut3</i> , <i>Chst4</i> , <i>Sept8</i> , <i>Gramd1c</i> , <i>Ccdc150</i> )
miR-1902	-1.54	0.0206	Distinct microRNA expression profiles in mouse renal cortical tissue [5].	92 ( <i>Tsc1</i> , <i>Spryd3</i> , <i>Lrtm1</i> , <i>Ndufs4</i> , <i>Calm1</i> )
miR-203	-1.45	0.0026	Lower in imatinib-resistant GBM cells [6]. Downregulated in colorectal cancer tissues [7].	483 ( <i>Sema3d</i> , <i>Lyzl1</i> , <i>Kat6b</i> , <i>Col22a1</i> , <i>Fbxo33</i> )
miR-376a	-1.44	0.0077	Downregulated in gastric cancer tissue [8].	06

miR-let-7a	-1.37	7.04E-05	Let-7a-5p was revealed to be downregulated by 21.67% in pneumoconiosis [9]. Downregulation promoted insulin receptor /insulin-like growth factor signaling in pancreatic ductal adenocarcinoma [10].	541
miR-148a	-1.34	0.0346	Downregulated in hypoxia condition of human colorectal cancer cell lines [11].	331
miR-362-3p	-1.33	0.0019	Aberrant miR-362-3p is associated with EBV-infection and prognosis in Nasopharyngeal Carcinoma [12].	883
miR-574-5p	-1.33	0.0182	Decreasing the HK-2 cells viability in acute kidney injury patients [13].	424
miR-134	-1.32	0.0178	Significantly downregulated in major depressive disorder [14].	173
miR-882	-1.31	0.0390	Osteoclastogenesis models has downregulated levels of miR-882 [15].	218
miR-678	-1.3	0.0113	No function reported.	6
mcmv-miR-m108-1	-1.29	0.0340	No function reported.	--
miR-423-5p	-1.28	0.0203	Effectively regulate the radiosensitivity in colorectal cancer [16].	216
miR-883a-3p	-1.27	0.0399	No function reported	273
miR-202-5p	-1.27	0.0493	Downregulated levels have a role in myocardial ischemia [17].	155
miR-let-7f	-1.26	0.0004	Early stages of epithelial ovarian cancer tissue and serum samples had reduced levels [18].	529
miR-187	-1.26	0.0298	Gastric cancer condition has downregulated levels of miR-187 [19].	21
miR-let-7c	-1.25	0.0036	Downregulation had a reported role in pathogenesis of human hepatocellular carcinoma [20].	558

miR-467e	-1.23	0.0483		83
miR-29b	-1.22	0.0048	Fibrous plaques of Peyronie's disease has downregulated expression [21].	452
miR-23a	-1.17	0.0186	Regulating the functions of inflammatory response in the septic insult condition [22].	546
miR-98	-1.14	0.0181	Reported functions of tumor development in pancreatic ductal adenocarcinoma [23].	541
miR-let-7e	-1.1	0.0155	Downregulated levels observed in the cerebral palsy condition [24].	538

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19 **Table S2.** Downregulated miRNAs during 16-weeks infection, molecular functions, and target  
20 genes.

miRNAs	Fold change	p-value	Reported functions	Number of Target Genes
miR-2135	-1.48	3.61E-05	Downregulated in the analgesic and addictive drug – morphine addiction [25].	--
miR-142-3p	-1.39	0.0226	Enhanced IFN- $\gamma$ expression observed in downregulated levels [26].	215 ( <i>Dcald</i> , <i>Rarg</i> , <i>Atg4c</i> , <i>Tbc1d2b</i> , <i>Fkbp1a</i> )
miR-130a	-1.25	0.0067	Oral squamous cell carcinoma can be controlled by downregulated levels [27].	366 ( <i>Zfp113</i> , <i>Slain1</i> , <i>Apcdd1</i> , <i>Sos2</i> , <i>Mtf1</i> )
miR-720	-1.24	0.0047	Promoting insulin secretion in MIN6 cells [28].	--
miR-1274a	-1.22	0.0137	Patients with colon cancer have increased survival rate on downregulated miR-1274a [29].	No target gene detected
miR-10a	-1.22	0.0236	Downregulated in the wound healing process [30].	178 ( <i>Nup50</i> , <i>Nr6a1</i> , <i>Epha5</i> , <i>Sobp</i> , <i>Wipf1</i> )
miR-151-3p	-1.21	2.87E-05	Mice with cardiac hypertrophy have downregulated levels of miR-151-3p [31].	57
miR-496	-1.21	0.0107	Gastric cancer cells of AGS and MKN45 has downregulated levels of miR-496 which affects AKT/mTOR signaling pathway [32].	113

miR-125b-5p	-1.2	0.0121	Small extracellular vesicles present in aging related diseases has downregulated expression of miR-125-5p levels [33].	496
miR-323-3p	-1.19	0.0169	Significant downregulation observed in Pancreatic ductal adenocarcinoma tissue and cell lines [34].	356
miR-195	-1.18	0.0176	Downregulated levels in hepatocellular carcinoma [35].	583
miR-582-5p	-1.16	0.0174	Bladder cancer cells and tissue has decreased expression [36].	396
miR-1944	-1.16	0.0176	Observed in cognitive impairment condition of Alzheimer's disease [37].	--
miR-106b	-1.16	0.0179	Attenuating the inflammation response in collagen-induced arthritis [38] and downregulated in mycobacterial infection [39].	761
miR-324-5p	-1.15	0.0173	Oxygen glucose deprivation mediated neurological injury has downregulated levels [40].	19
miR-15a	-1.11	0.0348	Downregulated levels observed in Apelin-mediated lung cancer development [41].	--
miR-16	-1.11	0.0465	Decreased the apoptotic rate in hypoxia/reoxygenation damage [42].	--
miR-25	-1.1	0.0275	Downregulated in the inflamed tracheal smooth muscle cells [43].	
miR-107	-1.1	0.0449	Downregulated miR-107 expression was associated with advanced Ann Arbor stage, high IPI score, LDH, and $\beta$ 2-MG level in DLBCL patients [13].	369

22 **Table S3.** Comparison of downregulated miRNAs between 8-weeks and 16-weeks of infection,  
 23 molecular functions, and target genes.

miRNAs	Fold change	p-value	Reported functions	Number of Target Genes
miR-2135	-1.77	0.0001	Downregulated in the analgesic and addictive drug – morphine [25].	No target gene detected
miR-2133	-1.58	0.0024	Downregulated in macrophage transition of M0 to M2a in microglia [44].	No target gene detected
miR-223	-1.57	0.0159	<i>Streptococcus</i> inflammation in murine macrophages decreased miR-223 levels [45].	222 ( <i>Orc4, Armcx1, Gpr155, Zbtb18, Pknox1</i> )
miR-142-3p	-1.44	0.0299	Enhanced IFN- $\gamma$ expression observed under downregulated levels [26].	215 ( <i>Dcakd, Rarg, Atg4c, Tbc1d2b, Fkbp1a</i> )
miR-130a	-1.35	0.0006	Oral squamous cell carcinoma can be controlled by downregulated levels [27].	366 ( <i>Zfp113, Slain1, Apcdd1, Sos2, Mtf1</i> )
miR-342-3p	-1.27	0.0077	Downregulated in Hepatocellular carcinoma condition [46].	309 ( <i>Apmmap, Prkaa2, Trim39, Sla, Pde6h</i> )
miR-496	-1.26	0.0006	Gastric cancer cells of AGS and MKN45 has downregulated levels of miR-496 which affecting AKT/mTOR signaling pathway [32].	113
miR-150	-1.25	0.0088	Myasthenia gravis condition has downregulated levels [47].	248
miR-720	-1.22	0.0019	Promoting insulin secretion in MIN6 cells [28].	--
miR-125b-5p	-1.22	0.0043	Small extracellular vesicles present in aging related diseases has downregulated expression of miR-125-5p levels [33].	496
miR-451	-1.21	0.0382	Downregulated in Nasopharyngeal carcinoma [48].	17
miR-15a	-1.18	0.01	Downregulated levels observed in Apelin- mediated lung cancer development [41].	--
miR-338-3p	-1.17	0.0492	Decreased levels observed in LO2 cells of hepatocellular carcinoma [49].	319
miR-1944	-1.16	0.0239	Observed in cognitive impairment condition of Alzheimer's disease [37].	--

miR-99a	-1.15	0.0313	Downregulation of miRNA 99a in oral squamous cell carcinomas contributes to the growth and survival of oral cancer cells [50].	15
miR-25	-1.13	0.0019	Downregulated in the inflamed tracheal smooth muscle cells [43].	369
miR-151-3p	-1.13	0.0092	Mice with cardiac hypertrophy demonstrated downregulated levels of miR-151-3p [31].	57
miR-324-5p	-1.07	0.0466	Oxygen glucose deprivation mediated neurological injury has downregulated levels [40].	19

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**Table S4.** miRTarBase analysis of upregulated DE microRNAs and their target genes in 8 weeks *T. denticola* infection.

miRTarBase ID	miRNA	Target gene
MIRT000604	mmu-miR-133a-3p	<i>Nfatc4</i>
MIRT001959	mmu-miR-133a-3p	<i>Runx2</i>
MIRT002895	mmu-miR-133a-3p	<i>Cdc42</i>
MIRT002896	mmu-miR-133a-3p	<i>Whsc2</i>
MIRT002897	mmu-miR-133a-3p	<i>Rhoa</i>
MIRT004022	mmu-miR-133a-3p	<i>Ucp2</i>
MIRT004102	mmu-miR-133a-3p	<i>Casp9</i>
MIRT004267	mmu-miR-133a-3p	<i>Spry1</i>
MIRT004652	mmu-miR-133a-3p	<i>Ccnd2</i>
MIRT004653	mmu-miR-133a-3p	<i>Srf</i>
MIRT004833	mmu-miR-133a-3p	<i>Hdac4</i>
MIRT005400	mmu-miR-133a-3p	<i>Pola1</i>
MIRT006261	mmu-miR-133a-3p	<i>Igf1r</i>
MIRT015113	mmu-miR-133a-5p	<i>Rhoa</i>
MIRT053603	mmu-miR-133a-3p	<i>Prdm16</i>
MIRT054781	mmu-miR-133a-3p	<i>Kcnmb1</i>
MIRT438724	mmu-miR-133a-3p	<i>Rapgef3</i>
MIRT438725	mmu-miR-133a-3p	<i>Prkacb</i>
MIRT438726	mmu-miR-133a-3p	<i>Adcy6</i>
MIRT438727	mmu-miR-133a-3p	<i>Adrb1</i>
MIRT593588	mmu-miR-133a-3p	<i>Zfp26</i>
MIRT594422	mmu-miR-133a-3p	<i>Gdf3</i>
MIRT599889	mmu-miR-133a-3p	<i>Acer1</i>
MIRT604592	mmu-miR-133a-3p	<i>Tnrc6b</i>
MIRT743586	mmu-miR-133a	<i>Acer1</i>
MIRT746521	mmu-miR-133a	<i>Tnrc6b</i>
MIRT748596	mmu-miR-133a	<i>Zfp26</i>
MIRT749511	mmu-miR-133a	<i>Gdf3</i>

We used mmu-miR-133 as an example for an upregulated DE miRNA during 8 weeks of infection in identifying the target genes using the miRTarBase. Each miRNA has different target genes and each with a specific MiRTarBase ID. *T. denticola*-infection induced DE upregulated mmu-miR-133 has 28 different target genes with 28 different MiRTarBase ID as stated in the table.

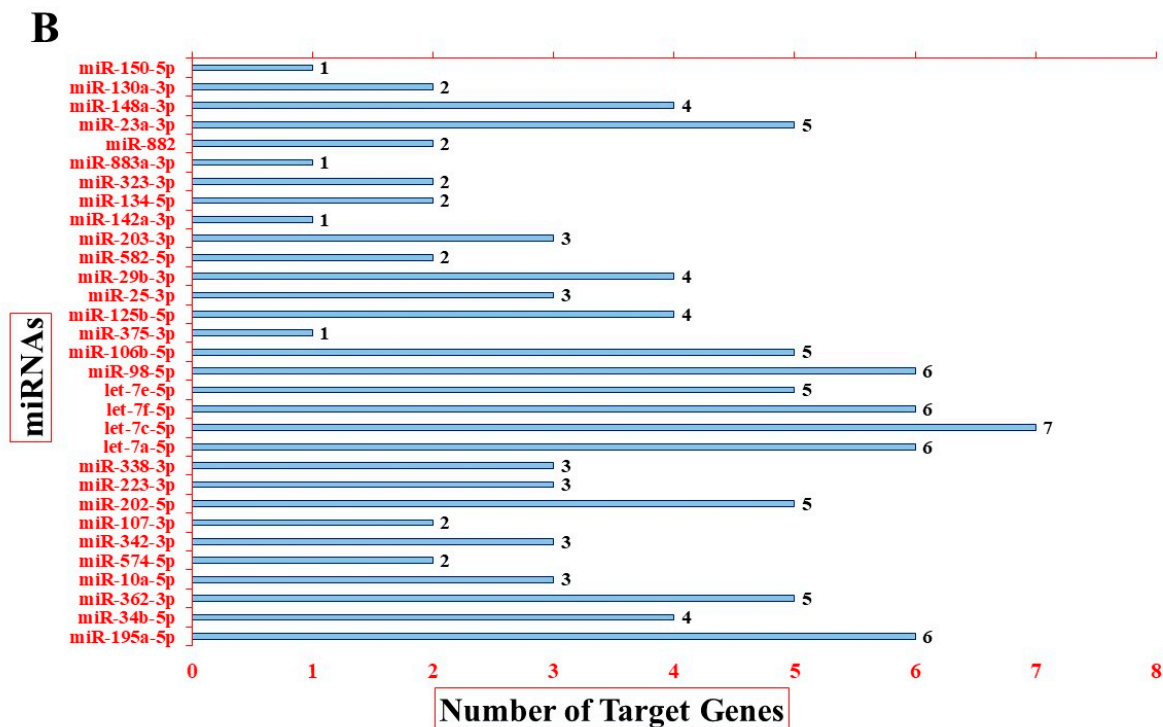
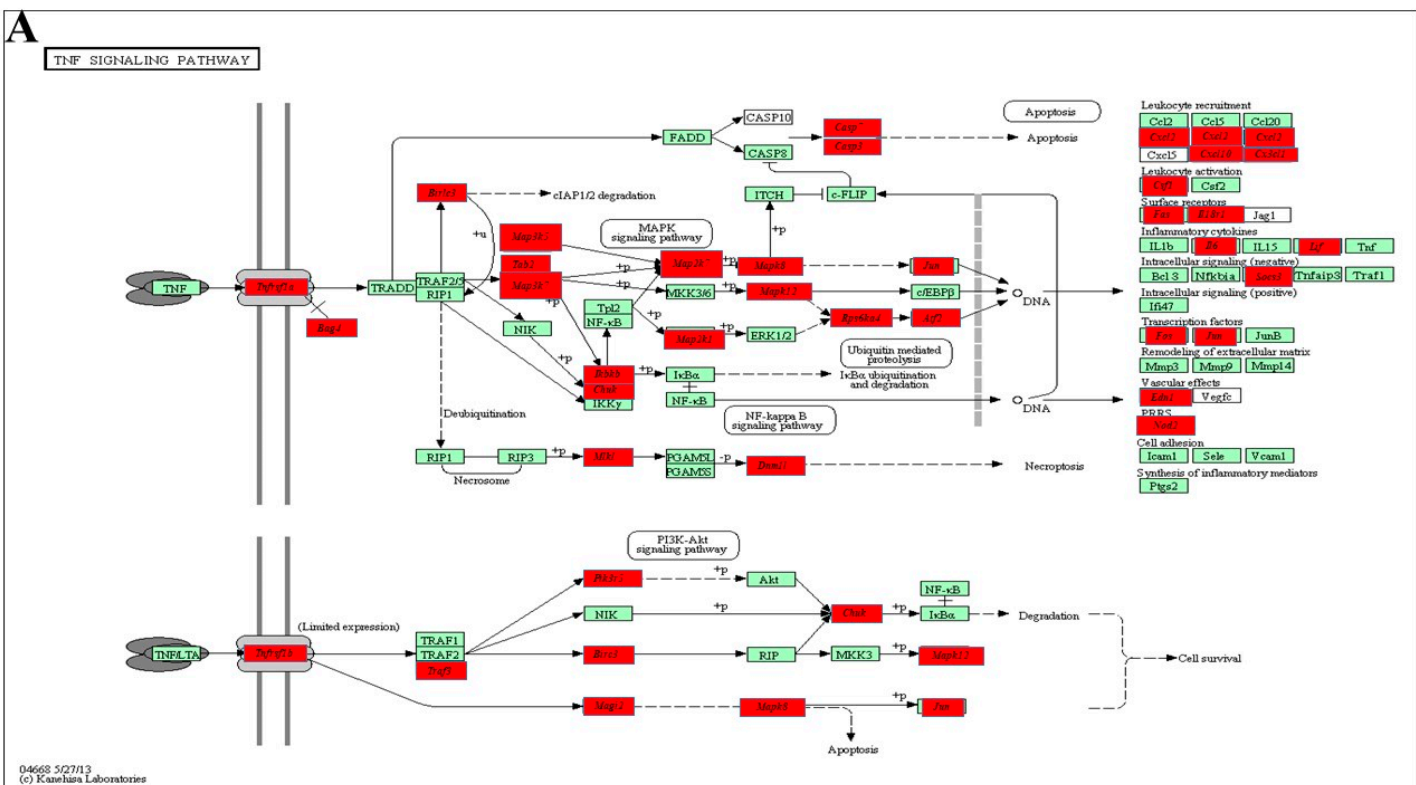
33 **Table S5.** miRTarBase analysis of upregulated DE microRNAs and their target genes in 16  
34 weeks *T. denticola* infection.

miRTarBase ID	miRNA	Target gene
MIRT744264	mmu-miR-486	<i>H2-Q4</i>
MIRT747084	mmu-miR-486	<i>Maoa</i>
MIRT750467	mmu-miR-486	<i>Zcchc9</i>
MIRT744588	mmu-miR-486	<i>Ms4a6c</i>
MIRT746127	mmu-miR-486	<i>Cnnm3</i>
MIRT747348	mmu-miR-486	<i>Tbc1d8b</i>
MIRT744650	mmu-miR-486	<i>Nkain3</i>
MIRT742609	mmu-miR-486	<i>Shc4</i>
MIRT749957	mmu-miR-486	<i>Tns3</i>
MIRT745593	mmu-miR-486	<i>Aim2</i>
MIRT748160	mmu-miR-486	<i>Gm7609</i>
MIRT753322	mmu-miR-486	<i>Fam129c</i>
MIRT598720	mmu-miR-486a-5p	<i>H2-Q4</i>
MIRT598358	mmu-miR-486a-5p	<i>Maoa</i>
MIRT590827	mmu-miR-486a-5p	<i>Zcchc9</i>
MIRT606321	mmu-miR-486a-5p	<i>Ms4a6c</i>
MIRT601041	mmu-miR-486a-5p	<i>Cnnm3</i>
MIRT597071	mmu-miR-486a-5p	<i>Tbc1d8b</i>
MIRT598042	mmu-miR-486a-5p	<i>Nkain3</i>
MIRT581056	mmu-miR-486a-5p	<i>Shc4</i>
MIRT592961	mmu-miR-486a-5p	<i>Tns3</i>
MIRT599803	mmu-miR-486a-5p	<i>Aim2</i>
MIRT598800	mmu-miR-486a-5p	<i>Gm7609</i>
MIRT578874	mmu-miR-486a-5p	<i>Fam129c</i>
MIRT003791	mmu-miR-486a-5p	<i>Pax7</i>
MIRT003527	mmu-miR-486a-5p	<i>Pten</i>
MIRT004586	mmu-miR-486a-5p	<i>Foxo1</i>
MIRT736452	mmu-miR-486a-5p	<i>Igf2bp3</i>
MIRT598721	mmu-miR-486b-5p	<i>H2-Q4</i>
MIRT598359	mmu-miR-486b-5p	<i>Maoa</i>
MIRT590828	mmu-miR-486b-5p	<i>Zcchc9</i>



MIRT606320	mmu-miR-486b-5p	<i>Ms4a6c</i>
MIRT601040	mmu-miR-486b-5p	<i>Cnnm3</i>
MIRT597070	mmu-miR-486b-5p	<i>Tbc1d8b</i>
MIRT598043	mmu-miR-486b-5p	<i>Nkain3</i>
MIRT581057	mmu-miR-486b-5p	<i>Shc4</i>
MIRT592960	mmu-miR-486b-5p	<i>Tns3</i>
MIRT599804	mmu-miR-486b-5p	<i>Aim2</i>
MIRT598799	mmu-miR-486b-5p	<i>Gm7609</i>
MIRT578873	mmu-miR-486b-5p	<i>Fam129c</i>
MIRT736777	mmu-miR-486b-3p	<i>Pten</i>

We used mmu-miR-486 an example for an upregulated DE miRNA during 16 weeks of infection in identifying the target genes using the miRTarBase. Each miRNA has different target genes and each with a specific MiRTarBase ID. *T. denticola*-infection induced DE upregulated mmu-miR-486 has 41 different target genes with 41 different MiRTarBase ID as stated in the table.



**Figure S1.** Significant differentially expressed (DE) genes (identified by KEGG) involved in the TNF signaling pathway (A). Red boxes indicate significantly altered expression of genes (e.g. leucocyte recruitment genes Cxcl2, Cxcl10; leucocyte activation gene Csf1; inflammatory cytokine genes IL-6, lif) based on *T. denticola*-induced miRNA profiles from Nanostring analysis. List of miRNAs and their target genes associated with TNF signaling pathway (B).

## 48    **References**

- 49    1.     Siow, M.Y.; Ng, L.P.; Vincent-Chong, V.K.; Jamaludin, M.; Abraham, M.T.; Abdul  
50       Rahman, Z.A.; Kallarakkal, T.G.; Yang, Y.H.; Cheong, S.C.; Zain, R.B. Dysregulation of  
51       miR-31 and miR-375 expression is associated with clinical outcomes in oral carcinoma.  
52       *Oral Dis* **2014**, *20*, 345-351, doi:10.1111/odi.12118.
- 53    2.     Mitani, Y.; Roberts, D.B.; Fatani, H.; Weber, R.S.; Kies, M.S.; Lippman, S.M.; El-Naggar,  
54       A.K. MicroRNA profiling of salivary adenoid cystic carcinoma: association of miR-17-92  
55       upregulation with poor outcome. *PLoS One* **2013**, *8*, e66778,  
56       doi:10.1371/journal.pone.0066778.
- 57    3.     Lu, Y.Y.; Zhang, X.J. MiR-34b-5p knockdown attenuates bleomycin-induced pulmonary  
58       fibrosis by targeting tissue inhibitor of metalloproteinase 3 (TIMP3). *Rivista europea per le*  
59       *scienze mediche e farmacologiche = European review for medical and pharmacological sciences.*  
60       **2019**, *23*, 2273-2279, doi:10.26355/eurrev\_201903\_17276.
- 61    4.     Parachuru, V.P.; Coates, D.E.; Milne, T.J.; Hussaini, H.M.; Rich, A.M.; Seymour, G.J.  
62       Forkhead box P3-positive regulatory T-cells and interleukin 17-positive T-helper 17 cells  
63       in chronic inflammatory periodontal disease. *J Periodontal Res* **2014**, *49*, 817-826,  
64       doi:10.1111/jre.12169.
- 65    5.     Schuler, E.; Parris, T.Z.; Helou, K.; Forssell-Aronsson, E. Distinct microRNA expression  
66       profiles in mouse renal cortical tissue after 177Lu-octreotate administration. *PLoS One*  
67       **2014**, *9*, e112645, doi:10.1371/journal.pone.0112645.
- 68    6.     Liao, H.Z.; Bai, Y.F.; Qiu, S.C.; Zheng, L.; Huang, L.Y.; Liu, T.Z.; Wang, X.; Liu, Y.T.; Xu,  
69       N.B.; Yan, X.H.; et al. MiR-203 downregulation is responsible for chemoresistance in  
70       human glioblastoma by promoting epithelial-mesenchymal transition via SNAIL2.  
71       *Oncotarget* **2015**, *6*, 8914-8928, doi:DOI 10.18632/oncotarget.3563.
- 72    7.     Deng, B.; Wang, B.; Fang, J.; Zhu, X.; Cao, Z.; Lin, Q.; Zhou, L.; Sun, X. MiRNA-203  
73       suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of  
74       EIF5A2. *Sci Rep* **2016**, *6*, 28301, doi:10.1038/srep28301.
- 75    8.     Zhang, C.; Liang, Y.; Ma, M.H.; Wu, K.Z.; Zhang, C.D.; Dai, D.Q. Downregulation of  
76       microRNA-376a in Gastric Cancer and Association with Poor Prognosis. *Cell Physiol*  
77       *Biochem* **2018**, *51*, 2010-2018, doi:10.1159/000495820.
- 78    9.     Zhang, L.; Hao, C.; Zhai, R.; Wang, D.; Zhang, J.; Bao, L.; Li, Y.; Yao, W. Downregulation  
79       of exosomal let-7a-5p in dust exposed- workers contributes to lung cancer development.  
80       *Respir Res* **2018**, *19*, 235, doi:10.1186/s12931-018-0949-y.
- 81    10.    Nweke, E.E.; Brand, M. Downregulation of the let-7 family of microRNAs may promote  
82       insulin receptor/insulin-like growth factor signalling pathways in pancreatic ductal  
83       adenocarcinoma. *Oncol Lett* **2020**, *20*, 2613-2620, doi:10.3892/ol.2020.11854.
- 84    11.    Nersisyan, S.; Galatenko, A.; Chekova, M.; Tonevitsky, A. Hypoxia-Induced miR-148a  
85       Downregulation Contributes to Poor Survival in Colorectal Cancer. *Front Genet* **2021**, *12*,  
86       662468, doi:10.3389/fgene.2021.662468.
- 87    12.    Wang, X.Y.; Chen, P. Aberrant miR-362-3p is Associated with EBV-Infection and  
88       Prognosis in Nasopharyngeal Carcinoma and Involved in Tumor Progression by  
89       Targeting JMJD2A. *Oncotargets and Therapy* **2022**, *15*, 121-131, doi:10.2147/Ott.S325100.
- 90    13.    Liu, S.; Zhao, L.; Zhang, L.; Qiao, L.; Gao, S. Downregulation of miR-574-5p inhibits HK-  
91       2 cell viability and predicts the onset of acute kidney injury in sepsis patients. *Ren Fail*  
92       **2021**, *43*, 942-948, doi:10.1080/0886022X.2021.1939051.

14. Zhang, H.P.; Liu, X.L.; Chen, J.J.; Cheng, K.; Bai, S.J.; Zheng, P.; Zhou, C.J.; Wang, W.; Wang, H.Y.; Zhong, L.M.; et al. Circulating microRNA 134 sheds light on the diagnosis of major depressive disorder. *Transl Psychiatry* **2020**, *10*, 95, doi:10.1038/s41398-020-0773-2.
15. Tian, Y.; Gong, Z.; Zhao, R.; Zhu, Y. Melatonin inhibits RANKL-induced osteoclastogenesis through the miR-882/Rev-erba axis in Raw264.7 cells. *Int J Mol Med* **2021**, *47*, 633-642, doi:10.3892/ijmm.2020.4820.
16. Shang, Y.; Wang, L.; Zhu, Z.; Gao, W.; Li, D.; Zhou, Z.; Chen, L.; Fu, C.G. Downregulation of miR-423-5p Contributes to the Radioresistance in Colorectal Cancer Cells. *Front Oncol* **2020**, *10*, 582239, doi:10.3389/fonc.2020.582239.
17. Li, Y.; Li, Q.; Zhang, O.; Guan, X.; Xue, Y.; Li, S.; Zhuang, X.; Zhou, B.; Miao, G. miR-202-5p protects rat against myocardial ischemia reperfusion injury by downregulating the expression of Trpv2 to attenuate the Ca (2+) overload in cardiomyocytes. *J Cell Biochem* **2019**, *120*, 13680-13693, doi:10.1002/jcb.28641.
18. Kumar, V.; Gupta, S.; Varma, K.; Chaurasia, A.; Sachan, M. Diagnostic performance of microRNA-34a, let-7f and microRNA-31 in epithelial ovarian cancer prediction. *J Gynecol Oncol* **2022**, *33*, e49, doi:10.3802/jgo.2022.33.e49.
19. Chen, W.; Cui, Y.; Wang, J.; Yuan, Y.; Sun, X.; Zhang, L.; Shen, S.; Cheng, J. Effects of downregulated expression of microRNA-187 in gastric cancer. *Exp Ther Med* **2018**, *16*, 1061-1070, doi:10.3892/etm.2018.6318.
20. Zhu, X.; Wu, L.; Yao, J.; Jiang, H.; Wang, Q.; Yang, Z.; Wu, F. MicroRNA let-7c Inhibits Cell Proliferation and Induces Cell Cycle Arrest by Targeting CDC25A in Human Hepatocellular Carcinoma. *PLoS One* **2015**, *10*, e0124266, doi:10.1371/journal.pone.0124266.
21. Dos Santos, V.G.; Dos Santos, G.A.; Neto, C.B.; Viana, N.I.; Pimenta, R.; Guimarães, V.R.; Candido, P.; Romão, P.; de Camargo, J.A.; Leite, K.R.M.; et al. Downregulation of miR-29b is associated with Peyronie's disease. *Urologia* **2022**, *89*, 451-455, doi:10.1177/03915603211036628.
22. Si, X.; Cao, D.; Chen, J.; Nie, Y.; Jiang, Z.; Chen, M.Y.; Wu, J.F.; Guan, X.D. miR-23a downregulation modulates the inflammatory response by targeting ATG12-mediated autophagy. *Mol Med Rep* **2018**, *18*, 1524-1530, doi:10.3892/mmr.2018.9081.
23. Fu, Y.; Liu, X.; Chen, Q.; Liu, T.; Lu, C.; Yu, J.; Miao, Y.; Wei, J. Downregulated miR-98-5p promotes PDAC proliferation and metastasis by reversely regulating MAP4K4. *J Exp Clin Cancer Res* **2018**, *37*, 130, doi:10.1186/s13046-018-0807-2.
24. Vechetti, I.J.; Norrbom, J.; Alkner, B.; Hjalmarsson, E.; Palmcrantz, A.; Pontén, E.; Pingel, J.; von Walden, F.; Fernandez-Gonzalo, R. Extracellular vesicle characteristics and microRNA content in cerebral palsy and typically developed individuals at rest and in response to aerobic exercise. *Front Physiol* **2022**, *13*, 1072040, doi:10.3389/fphys.2022.1072040.
25. Wang, T.; Chen, X.; Zeng, K. Molecular mechanism and candidate biomarkers of morphine for analgesia and addiction effects. *Ann Transl Med* **2022**, *10*, 89, doi:10.21037/atm-21-7037.
26. Ma, N.; Wei, T.; Wang, B.; Jiang, X.; Zhou, L.; Zhong, R. MicroRNA-142-3p inhibits IFN-γ production via targeting of RICTOR in. *Ann Transl Med* **2019**, *7*, 649, doi:10.21037/atm.2019.10.85.
27. Peng, Y.; Hu, S.; Zhang, K.; Wang, Y.; Rouzi, M.; Zhou, D.; Yang, R. Downregulation of MicroRNA-130a Inhibits Oral Squamous Cell Carcinoma Proliferation and Metastasis via the Hippo-YAP Pathway. *Cancer Manag Res* **2021**, *13*, 4829-4840, doi:10.2147/CMAR.S287575.

- 141 28. Lu, C.; Wang, D.; Feng, Y.; Feng, L.; Li, Z. miR-720 Regulates Insulin Secretion by  
142 Targeting Rab35. *Biomed Res Int* **2021**, 2021, 6662612, doi:10.1155/2021/6662612.
- 143 29. Ren, B.; Yang, B.; Li, P.; Ge, L. Upregulation of MiR-1274a is Correlated with Survival  
144 Outcomes and Promotes Cell Proliferation, Migration, and Invasion of Colon Cancer.  
145 *Onco Targets Ther* **2020**, 13, 6957-6966, doi:10.2147/OTT.S246160.
- 146 30. Simões, A.; Chen, L.; Chen, Z.; Zhao, Y.; Gao, S.; Marucha, P.T.; Dai, Y.; DiPietro, L.A.;  
147 Zhou, X. Differential microRNA profile underlies the divergent healing responses in skin  
148 and oral mucosal wounds. *Sci Rep* **2019**, 9, 7160, doi:10.1038/s41598-019-43682-w.
- 149 31. Wei, H.; Li, Z.; Wang, X.; Wang, J.; Pang, W.; Yang, G.; Shen, Q.W. microRNA-151-3p  
150 regulates slow muscle gene expression by targeting ATP2a2 in skeletal muscle cells. *J Cell*  
151 *Physiol* **2015**, 230, 1003-1012, doi:10.1002/jcp.24793.
- 152 32. Su, R.; Zhao, E.; Zhang, J. miR-496 inhibits proliferation via LYN and AKT pathway in  
153 gastric cancer. *Open Med (Wars)* **2021**, 16, 1206-1214, doi:10.1515/med-2021-0313.
- 154 33. Kim, C.G.; Lee, J.K.; Cho, G.J.; Shin, O.S.; Gim, J.A. Small RNA sequencing of small  
155 extracellular vesicles secreted by umbilical cord mesenchymal stem cells following  
156 replicative senescence. *Genes Genomics* **2023**, 45, 347-358, doi:10.1007/s13258-022-01297-y.
- 157 34. Wang, C.; Liu, P.; Wu, H.; Cui, P.; Li, Y.; Liu, Y.; Liu, Z.; Gou, S. MicroRNA-323-3p inhibits  
158 cell invasion and metastasis in pancreatic ductal adenocarcinoma via direct suppression  
159 of SMAD2 and SMAD3. *Oncotarget* **2016**, 7, 14912-14924, doi:10.18632/oncotarget.7482.
- 160 35. Yu, S.; Jing, L.; Yin, X.R.; Wang, M.C.; Chen, Y.M.; Guo, Y.; Nan, K.J.; Han, L.L. MiR-195  
161 suppresses the metastasis and epithelial-mesenchymal transition of hepatocellular  
162 carcinoma by inhibiting YAP. *Oncotarget* **2017**, 8, 99757-99771,  
163 doi:10.18632/oncotarget.20909.
- 164 36. Tian, Y.; Guan, Y.; Su, Y.; Luo, W.; Yang, G.; Zhang, Y. MiR-582-5p Inhibits Bladder  
165 Cancer-Genesis by Suppressing TTK Expression. *Cancer Manag Res* **2020**, 12, 11933-11944,  
166 doi:10.2147/CMAR.S274835.
- 167 37. Chum, P.P.; Hakim, M.A.; Behringer, E.J. Cerebrovascular microRNA Expression Profile  
168 During Early Development of Alzheimer's Disease in a Mouse Model. *J Alzheimers Dis*  
169 **2022**, 85, 91-113, doi:10.3233/JAD-215223.
- 170 38. Tao, Y.; Wang, Z.; Wang, L.; Shi, J.; Guo, X.; Zhou, W.; Wu, X.; Liu, Y.; Zhang, W.; Yang,  
171 H.; et al. Downregulation of miR-106b attenuates inflammatory responses and joint  
172 damage in collagen-induced arthritis. *Rheumatology (Oxford)* **2017**, 56, 1804-1813,  
173 doi:10.1093/rheumatology/kex233.
- 174 39. Pires, D.; Bernard, E.M.; Pombo, J.P.; Carmo, N.; Fialho, C.; Gutierrez, M.G.; Bettencourt,  
175 P.; Anes, E. Modulates miR-106b-5p to Control Cathepsin S Expression Resulting in  
176 Higher Pathogen Survival and Poor T-Cell Activation. *Front Immunol* **2017**, 8, 1819,  
177 doi:10.3389/fimmu.2017.01819.
- 178 40. Gu, J.; Gui, S.; Hu, L.; Kong, L.; Di, M.; Wang, Y. Downregulated miRNA-324-5p  
179 aggravates neuronal injury induced by oxygen-glucose deprivation via modulating RAN.  
180 *Exp Ther Med* **2020**, 19, 658-664, doi:10.3892/etm.2019.8249.
- 181 41. Ran, J.; Li, Y.; Liu, L.; Zhu, Y.; Ni, Y.; Huang, H.; Liu, Z.; Miao, Z.; Zhang, L. Apelin  
182 enhances biological functions in lung cancer A549 cells by downregulating exosomal miR-  
183 15a-5p. *Carcinogenesis* **2021**, 42, 243-253, doi:10.1093/carcin/bgaa089.
- 184 42. Zhang, H.J.; Zhang, Y.N.; Teng, Z.Y. Downregulation of miR-16 protects H9c2(2-1) cells  
185 against hypoxia/reoxygenation damage by targeting CIAPIN1 and regulating the NF-κB  
186 pathway. *Mol Med Rep* **2019**, 20, 3113-3122, doi:10.3892/mmr.2019.10568.
- 187 43. Sárközy, M.; Kahán, Z.; Csont, T. A myriad of roles of miR-25 in health and disease.  
188 *Oncotarget* **2018**, 9, 21580-21612, doi:10.18632/oncotarget.24662.

44. Freilich, R.W.; Woodbury, M.E.; Ikezu, T. Integrated expression profiles of mRNA and miRNA in polarized primary murine microglia. *PLoS One* **2013**, *8*, e79416, doi:10.1371/journal.pone.0079416.
45. Li, G.; Zong, X.; Cheng, Y.; Xu, J.; Deng, J.; Huang, Y.; Ma, C.; Fu, Q. miR-223-3p contributes to suppressing NLRP3 inflammasome activation in *Streptococcus equi* ssp. *zooepidemicus* infection. *Vet Microbiol* **2022**, *269*, 109430, doi:10.1016/j.vetmic.2022.109430.
46. Komoll, R.M.; Hu, Q.; Olarewaju, O.; von Döhlen, L.; Yuan, Q.; Xie, Y.; Tsay, H.C.; Daon, J.; Qin, R.; Manns, M.P.; et al. MicroRNA-342-3p is a potent tumour suppressor in hepatocellular carcinoma. *J Hepatol* **2021**, *74*, 122-134, doi:10.1016/j.jhep.2020.07.039.
47. Cron, M.A.; Maillard, S.; Truffault, F.; Gualeni, A.V.; Gloghini, A.; Fadel, E.; Guihaire, J.; Behin, A.; Berrih-Aknin, S.; Le Panse, R. Causes and Consequences of miR-150-5p Dysregulation in Myasthenia Gravis. *Front Immunol* **2019**, *10*, 539, doi:10.3389/fimmu.2019.00539.
48. Liu, N.; Jiang, N.; Guo, R.; Jiang, W.; He, Q.M.; Xu, Y.F.; Li, Y.Q.; Tang, L.L.; Mao, Y.P.; Sun, Y.; et al. MiR-451 inhibits cell growth and invasion by targeting MIF and is associated with survival in nasopharyngeal carcinoma. *Mol Cancer* **2013**, *12*, 123, doi:10.1186/1476-4598-12-123.
49. Fu, X.; Tan, D.; Hou, Z.; Hu, Z.; Liu, G. miR-338-3p is down-regulated by hepatitis B virus X and inhibits cell proliferation by targeting the 3'-UTR region of CyclinD1. *Int J Mol Sci* **2012**, *13*, 8514-8539, doi:10.3390/ijms13078514.
50. Yan, B.; Fu, Q.; Lai, L.; Tao, X.; Fei, Y.; Shen, J.; Chen, Z.; Wang, Q. Downregulation of microRNA 99a in oral squamous cell carcinomas contributes to the growth and survival of oral cancer cells. *Mol Med Rep* **2012**, *6*, 675-681, doi:10.3892/mmr.2012.971.