**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 *(Bmpr2, Mtpn, Klf4, Enah, Fzd8, F10, Zfpm2, Atxn7, Rs1, Tsc1, Pdpk1, Uvssa, Nufip2)* |
| 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 *(Arhgap1, Ppp4r2, Dixdc1, Htr2c, Rpap1, N4bp1, Tbc1d2b, Rab3c)* |
| miR-210 | -1.55 | 0.0095 | Induces endothelial dysfunction in type 2 diabetes. Promoting regulatory T-cell signaling in periodontitis [4]. | 16 *(Onecut3, Chst4, Sept8, Gramd1c, Ccdc150)* |
| miR-1902 | -1.54 | 0.0206 | Distinct microRNA expression profiles in mouse renal cortical tissue [5]. | 92 *(Tsc1, Spryd3, Lrtm1, Ndufs4, Calm1)* |
| miR-203 | -1.45 | 0.0026 | Lower in imatinib-resistant GBM cells [6]. Downregulated in colorectal cancer tissues [7]. | 483 *(Sema3d, Lyzl1, Kat6b, Col22a1, Fbxo33)* |
| 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 |

**Table S2.** Downregulated miRNAs during 16-weeks infection, molecular functions, and target 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-γ expression observed in downregulated levels [26].  | 215 *(Dcakd, Rarg, Atg4c, Tbc1d2b, Fkbp1a)* |
| miR-130a | -1.25 | 0.0067 | Oral squamous cell carcinoma can be controlled by downregulated levels [27]. | 366 *(Zfp113, Slain1, Apcdd1, Sos2, Mtf1)* |
| 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 *(Nup50, Nr6a1, Epha5, Sobp, Wipf1)*  |
| 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 inflammed 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 β2-MG level in DLBCL patients [13]. | 369 |

**Table S3.** Comparison of downregulated miRNAs between 8-weeks and 16-weeks of infection, 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 | *Streptococcus* inflammation in murine macrophages decreased miR-223 levels [45]. | 222 *(Orc4, Armcx1, Gpr155, Zbtb18, Pknox1)* |
| miR-142-3p | -1.44 | 0.0299 | Enhanced IFN-γ expression observed under downregulated levels [26]. | *215* (*Dcakd, Rarg, Atg4c, Tbc1d2b, Fkbp1a)* |
| miR-130a | -1.35 | 0.0006 | Oral squamous cell carcinoma can be controlled by downregulated levels [27]. |  366 (*Zfp113, Slain1, Apcdd1, Sos2, Mtf1)* |
| miR-342-3p | -1.27 | 0.0077 | Downregulated in Hepatocellular carcinoma condition [46]. | 309 (*Apmap, Prkaa2, Trim39, Sla, Pde6h*) |
| 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 |

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

|  |  |  |
| --- | --- | --- |
| **miRTarBase ID** | **miRNA** | **Target gene** |
| [MIRT000604](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT000604) | mmu-miR-133a-3p | *Nfatc4* |
| [MIRT001959](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT001959) | mmu-miR-133a-3p | *Runx2* |
| [MIRT002895](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT002895) | mmu-miR-133a-3p | *Cdc42* |
| [MIRT002896](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT002896) | mmu-miR-133a-3p | *Whsc2* |
| [MIRT002897](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT002897) | mmu-miR-133a-3p | *Rhoa* |
| [MIRT004022](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004022) | mmu-miR-133a-3p | *Ucp2* |
| [MIRT004102](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004102) | mmu-miR-133a-3p | *Casp9* |
| [MIRT004267](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004267) | mmu-miR-133a-3p | *Spry1* |
| [MIRT004652](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004652) | mmu-miR-133a-3p | *Ccnd2* |
| [MIRT004653](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004653) | mmu-miR-133a-3p | *Srf* |
| [MIRT004833](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT004833) | mmu-miR-133a-3p | *Hdac4* |
| [MIRT005400](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT005400) | mmu-miR-133a-3p | *Pola1* |
| [MIRT006261](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT006261) | mmu-miR-133a-3p | *Igf1r* |
| [MIRT015113](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT015113) | mmu-miR-133a-5p | *Rhoa* |
| [MIRT053603](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT053603) | mmu-miR-133a-3p | *Prdm16* |
| [MIRT054781](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT054781) | mmu-miR-133a-3p | *Kcnmb1* |
| [MIRT438724](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT438724) | mmu-miR-133a-3p | *Rapgef3* |
| [MIRT438725](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT438725) | mmu-miR-133a-3p | *Prkacb* |
| [MIRT438726](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT438726) | mmu-miR-133a-3p | *Adcy6* |
| [MIRT438727](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT438727) | mmu-miR-133a-3p | *Adrb1* |
| [MIRT593588](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT593588) | mmu-miR-133a-3p | *Zfp26* |
| [MIRT594422](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT594422) | mmu-miR-133a-3p | *Gdf3* |
| [MIRT599889](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT599889) | mmu-miR-133a-3p | *Acer1* |
| [MIRT604592](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT604592) | mmu-miR-133a-3p | *Tnrc6b* |
| [MIRT743586](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT743586) | mmu-miR-133a | *Acer1* |
| [MIRT746521](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT746521) | mmu-miR-133a | *Tnrc6b* |
| [MIRT748596](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT748596) | mmu-miR-133a | *Zfp26* |
| [MIRT749511](https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/detail.php?mirtid=MIRT749511) | mmu-miR-133a | *Gdf3* |

We used mmu-miR-133 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.

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

|  |  |  |
| --- | --- | --- |
| **miRTarBase ID** | **miRNA** | **Target gene** |
| MIRT744264 | mmu-miR-486 | *H2-Q4* |
| MIRT747084 | mmu-miR-486 | *Maoa* |
| MIRT750467 | mmu-miR-486 | *Zcchc9* |
| MIRT744588 | mmu-miR-486 | *Ms4a6c* |
| MIRT746127 | mmu-miR-486 | *Cnnm3* |
| MIRT747348 | mmu-miR-486 | *Tbc1d8b* |
| MIRT744650 | mmu-miR-486 | *Nkain3* |
| MIRT742609 | mmu-miR-486 | *Shc4* |
| MIRT749957 | mmu-miR-486 | *Tns3* |
| MIRT745593 | mmu-miR-486 | *Aim2* |
| MIRT748160 | mmu-miR-486 | *Gm7609* |
| MIRT753322 | mmu-miR-486 | *Fam129c* |
| MIRT598720 | mmu-miR-486a-5p | *H2-Q4* |
| MIRT598358 | mmu-miR-486a-5p | *Maoa* |
| MIRT590827 | mmu-miR-486a-5p | *Zcchc9* |
| MIRT606321 | mmu-miR-486a-5p | *Ms4a6c* |
| MIRT601041 | mmu-miR-486a-5p | *Cnnm3* |
| MIRT597071 | mmu-miR-486a-5p | *Tbc1d8b* |
| MIRT598042 | mmu-miR-486a-5p | *Nkain3* |
| MIRT581056 | mmu-miR-486a-5p | *Shc4* |
| MIRT592961 | mmu-miR-486a-5p | *Tns3* |
| MIRT599803 | mmu-miR-486a-5p | *Aim2* |
| MIRT598800 | mmu-miR-486a-5p | *Gm7609* |
| MIRT578874 | mmu-miR-486a-5p | *Fam129c* |
| MIRT003791 | mmu-miR-486a-5p | *Pax7* |
| MIRT003527 | mmu-miR-486a-5p | *Pten* |
| MIRT004586 | mmu-miR-486a-5p | *Foxo1* |
| MIRT736452 | mmu-miR-486a-5p | *Igf2bp3* |
| MIRT598721 | mmu-miR-486b-5p | *H2-Q4* |
| MIRT598359 | mmu-miR-486b-5p | *Maoa* |
| MIRT590828 | mmu-miR-486b-5p | *Zcchc9* |
| MIRT606320 | mmu-miR-486b-5p | *Ms4a6c* |
| MIRT601040 | mmu-miR-486b-5p | *Cnnm3* |
| MIRT597070 | mmu-miR-486b-5p | *Tbc1d8b* |
| MIRT598043 | mmu-miR-486b-5p | *Nkain3* |
| MIRT581057 | mmu-miR-486b-5p | *Shc4* |
| MIRT592960 | mmu-miR-486b-5p | *Tns3* |
| MIRT599804 | mmu-miR-486b-5p | *Aim2* |
| MIRT598799 | mmu-miR-486b-5p | *Gm7609* |
| MIRT578873 | mmu-miR-486b-5p | *Fam129c* |
| MIRT736777 | mmu-miR-486b-3p | *Pten* |

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).

**References**

1. Siow, M.Y.; Ng, L.P.; Vincent-Chong, V.K.; Jamaludin, M.; Abraham, M.T.; Abdul Rahman, Z.A.; Kallarakkal, T.G.; Yang, Y.H.; Cheong, S.C.; Zain, R.B. Dysregulation of miR-31 and miR-375 expression is associated with clinical outcomes in oral carcinoma. *Oral Dis* **2014**, *20*, 345-351, doi:10.1111/odi.12118.

2. Mitani, Y.; Roberts, D.B.; Fatani, H.; Weber, R.S.; Kies, M.S.; Lippman, S.M.; El-Naggar, A.K. MicroRNA profiling of salivary adenoid cystic carcinoma: association of miR-17-92 upregulation with poor outcome. *PLoS One* **2013**, *8*, e66778, doi:10.1371/journal.pone.0066778.

3. Lu, Y.Y.; Zhang, X.J. MiR-34b-5p knockdown attenuates bleomycin-induced pulmonary fibrosis by targeting tissue inhibitor of metalloproteinase 3 (TIMP3). *Rivista europea per le scienze mediche e farmacologiche = European review for medical and pharmacological sciences.* **2019**, *23*, 2273-2279, doi:10.26355/eurrev\_201903\_17276.

4. Parachuru, V.P.; Coates, D.E.; Milne, T.J.; Hussaini, H.M.; Rich, A.M.; Seymour, G.J. Forkhead box P3-positive regulatory T-cells and interleukin 17-positive T-helper 17 cells in chronic inflammatory periodontal disease. *J Periodontal Res* **2014**, *49*, 817-826, doi:10.1111/jre.12169.

5. Schuler, E.; Parris, T.Z.; Helou, K.; Forssell-Aronsson, E. Distinct microRNA expression profiles in mouse renal cortical tissue after 177Lu-octreotate administration. *PLoS One* **2014**, *9*, e112645, doi:10.1371/journal.pone.0112645.

6. Liao, H.Z.; Bai, Y.F.; Qiu, S.C.; Zheng, L.; Huang, L.Y.; Liu, T.Z.; Wang, X.; Liu, Y.T.; Xu, N.B.; Yan, X.H.; et al. MiR-203 downregulation is responsible for chemoresistance in human glioblastoma by promoting epithelial-mesenchymal transition via SNAI2. *Oncotarget* **2015**, *6*, 8914-8928, doi:DOI 10.18632/oncotarget.3563.

7. Deng, B.; Wang, B.; Fang, J.; Zhu, X.; Cao, Z.; Lin, Q.; Zhou, L.; Sun, X. MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2. *Sci Rep* **2016**, *6*, 28301, doi:10.1038/srep28301.

8. Zhang, C.; Liang, Y.; Ma, M.H.; Wu, K.Z.; Zhang, C.D.; Dai, D.Q. Downregulation of microRNA-376a in Gastric Cancer and Association with Poor Prognosis. *Cell Physiol Biochem* **2018**, *51*, 2010-2018, doi:10.1159/000495820.

9. Zhang, L.; Hao, C.; Zhai, R.; Wang, D.; Zhang, J.; Bao, L.; Li, Y.; Yao, W. Downregulation of exosomal let-7a-5p in dust exposed- workers contributes to lung cancer development. *Respir Res* **2018**, *19*, 235, doi:10.1186/s12931-018-0949-y.

10. Nweke, E.E.; Brand, M. Downregulation of the let-7 family of microRNAs may promote insulin receptor/insulin-like growth factor signalling pathways in pancreatic ductal adenocarcinoma. *Oncol Lett* **2020**, *20*, 2613-2620, doi:10.3892/ol.2020.11854.

11. Nersisyan, S.; Galatenko, A.; Chekova, M.; Tonevitsky, A. Hypoxia-Induced miR-148a Downregulation Contributes to Poor Survival in Colorectal Cancer. *Front Genet* **2021**, *12*, 662468, doi:10.3389/fgene.2021.662468.

12. Wang, X.Y.; Chen, P. Aberrant miR-362-3p is Associated with EBV-Infection and Prognosis in Nasopharyngeal Carcinoma and Involved in Tumor Progression by Targeting JMJD2A. *Oncotargets and Therapy* **2022**, *15*, 121-131, doi:10.2147/Ott.S325100.

13. Liu, S.; Zhao, L.; Zhang, L.; Qiao, L.; Gao, S. Downregulation of miR-574-5p inhibits HK-2 cell viability and predicts the onset of acute kidney injury in sepsis patients. *Ren Fail* **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‑erbα 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.

28. Lu, C.; Wang, D.; Feng, Y.; Feng, L.; Li, Z. miR-720 Regulates Insulin Secretion by Targeting Rab35. *Biomed Res Int* **2021**, *2021*, 6662612, doi:10.1155/2021/6662612.

29. Ren, B.; Yang, B.; Li, P.; Ge, L. Upregulation of MiR-1274a is Correlated with Survival Outcomes and Promotes Cell Proliferation, Migration, and Invasion of Colon Cancer. *Onco Targets Ther* **2020**, *13*, 6957-6966, doi:10.2147/OTT.S246160.

30. Simões, A.; Chen, L.; Chen, Z.; Zhao, Y.; Gao, S.; Marucha, P.T.; Dai, Y.; DiPietro, L.A.; Zhou, X. Differential microRNA profile underlies the divergent healing responses in skin and oral mucosal wounds. *Sci Rep* **2019**, *9*, 7160, doi:10.1038/s41598-019-43682-w.

31. Wei, H.; Li, Z.; Wang, X.; Wang, J.; Pang, W.; Yang, G.; Shen, Q.W. microRNA-151-3p regulates slow muscle gene expression by targeting ATP2a2 in skeletal muscle cells. *J Cell Physiol* **2015**, *230*, 1003-1012, doi:10.1002/jcp.24793.

32. Su, R.; Zhao, E.; Zhang, J. miR-496 inhibits proliferation via LYN and AKT pathway in gastric cancer. *Open Med (Wars)* **2021**, *16*, 1206-1214, doi:10.1515/med-2021-0313.

33. Kim, C.G.; Lee, J.K.; Cho, G.J.; Shin, O.S.; Gim, J.A. Small RNA sequencing of small extracellular vesicles secreted by umbilical cord mesenchymal stem cells following replicative senescence. *Genes Genomics* **2023**, *45*, 347-358, doi:10.1007/s13258-022-01297-y.

34. Wang, C.; Liu, P.; Wu, H.; Cui, P.; Li, Y.; Liu, Y.; Liu, Z.; Gou, S. MicroRNA-323-3p inhibits cell invasion and metastasis in pancreatic ductal adenocarcinoma via direct suppression of SMAD2 and SMAD3. *Oncotarget* **2016**, *7*, 14912-14924, doi:10.18632/oncotarget.7482.

35. Yu, S.; Jing, L.; Yin, X.R.; Wang, M.C.; Chen, Y.M.; Guo, Y.; Nan, K.J.; Han, L.L. MiR-195 suppresses the metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma by inhibiting YAP. *Oncotarget* **2017**, *8*, 99757-99771, doi:10.18632/oncotarget.20909.

36. Tian, Y.; Guan, Y.; Su, Y.; Luo, W.; Yang, G.; Zhang, Y. MiR-582-5p Inhibits Bladder Cancer-Genesis by Suppressing TTK Expression. *Cancer Manag Res* **2020**, *12*, 11933-11944, doi:10.2147/CMAR.S274835.

37. Chum, P.P.; Hakim, M.A.; Behringer, E.J. Cerebrovascular microRNA Expression Profile During Early Development of Alzheimer's Disease in a Mouse Model. *J Alzheimers Dis* **2022**, *85*, 91-113, doi:10.3233/JAD-215223.

38. Tao, Y.; Wang, Z.; Wang, L.; Shi, J.; Guo, X.; Zhou, W.; Wu, X.; Liu, Y.; Zhang, W.; Yang, H.; et al. Downregulation of miR-106b attenuates inflammatory responses and joint damage in collagen-induced arthritis. *Rheumatology (Oxford)* **2017**, *56*, 1804-1813, doi:10.1093/rheumatology/kex233.

39. Pires, D.; Bernard, E.M.; Pombo, J.P.; Carmo, N.; Fialho, C.; Gutierrez, M.G.; Bettencourt, P.; Anes, E. Modulates miR-106b-5p to Control Cathepsin S Expression Resulting in Higher Pathogen Survival and Poor T-Cell Activation. *Front Immunol* **2017**, *8*, 1819, doi:10.3389/fimmu.2017.01819.

40. Gu, J.; Gui, S.; Hu, L.; Kong, L.; Di, M.; Wang, Y. Downregulated miRNA-324-5p aggravates neuronal injury induced by oxygen-glucose deprivation via modulating RAN. *Exp Ther Med* **2020**, *19*, 658-664, doi:10.3892/etm.2019.8249.

41. Ran, J.; Li, Y.; Liu, L.; Zhu, Y.; Ni, Y.; Huang, H.; Liu, Z.; Miao, Z.; Zhang, L. Apelin enhances biological functions in lung cancer A549 cells by downregulating exosomal miR-15a-5p. *Carcinogenesis* **2021**, *42*, 243-253, doi:10.1093/carcin/bgaa089.

42. Zhang, H.J.; Zhang, Y.N.; Teng, Z.Y. Downregulation of miR‑16 protects H9c2(2‑1) cells against hypoxia/reoxygenation damage by targeting CIAPIN1 and regulating the NF‑κB pathway. *Mol Med Rep* **2019**, *20*, 3113-3122, doi:10.3892/mmr.2019.10568.

43. Sárközy, M.; Kahán, Z.; Csont, T. A myriad of roles of miR-25 in health and disease. *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.