Review

BDNF Modulation by microRNAs: An Update on the Experimental Evidence

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Review

BDNF Modulation by microRNAs: An Update on the *Experimental* Evidence

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Abstract: MicroRNAs can interfere with a protein function by suppressing their messenger RNA translation or the synthesis of its related factors. The function of brain-derived neurotrophic factor (BDNF) is essential to the proper formation and function of the nervous system and is seen to be regulated by many microRNAs. However, understanding how microRNAs influence BDNF actions within cells requires a wider comprehension of their integrative regulatory mechanisms. **Aim:** In this literature review, we have synthesized the evidence of microRNA regulation on BDNF in cells and tissues, and provided an analytical discussion about direct and indirect mechanisms that appeared involved in BDNF regulation by microRNAs. **Methods:** Searches were conducted on PubMed.gov using the terms "BDNF" AND "MicroRNA" and "brain-derived neurotrophic factor" AND "MicroRNA", updated on September 1st, 2023. Papers without open access were requested from the authors. One hundred and seventy-one papers were included for review and discussion. Results and **Discussion:** The local regulation of BDNF by microRNAs involves a complex interaction between a series of microRNAs with target proteins that can either inhibit or enhance BDNF expression, at the core of cell metabolism. Therefore, understanding this homeostatic balance provides resources for the future development of vector-delivery-based therapies for the neuroprotective effects of BDNF.

Keywords: BDNF; microRNA; regenerative medicine; neuroprotection

Introduction

MicroRNAs are a class of non-coding RNAs which do not code for proteins but carry out biological function by regulating cell proteome at the translational level. They can be expressed within the activation of a gene promoter or their own promoters (Lai, 2002; Smallridge, 2001), and play a regulatory role in protein synthesis by targeting and degrading RNA transcripts containing compatible nucleotide sequences (Gulyaeva & Kushlinskiy, 2016; Ha & Kim, 2014; Y. Lee et al., 2004; O'Brien et al., 2018; Shukla et al., 2011). MicroRNAs are seen to participate in the functional regulation at the distant synaptic sites in neuronal cells, and to modulate inflammatory mechanisms that lead to neurological diseases (Chen et al., 2024; Kaurani, 2024).

As a main expressed neurotrophin, the brain-derived neurotrophic factor (BDNF) plays essential roles in the development and maintenance of neural tissues (Labrador-Velandia et al., 2019; Trzaska et al., 2009). Signaling of the mature form of BDNF via tropomyosin receptor kinase (Trk) B, participates in neuronal survival, dendritogenesis, synaptogenesis, axon growth and synaptic function; meanwhile, release pro-BDNF isoform can bind with low affinity to p75 neurotrophin receptor (p75NTR) and lead to apoptosis. So that, a tight regulation of BDNF activity is necessary for the proper functioning of the central nervous system (CNS) (Bouron et al., 2006; de Assis & Hoffman, 2022; Ibarra et al., 2022).

Analyses *in silico* estimate hundreds of microRNAs as possible regulators of BDNF. However, with a 10–20% variability detected in predicted regulatory relationships between genes and microRNAs in human RefSeq data set, the effective regulation of BDNF mRNA transcripts by

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microRNAs in biological systems is much smaller (Rajewsky, 2006). In addition, the microRNA affinity for multiple targets and microRNA-microRNA interactions in a cell milieu influence on their regulation and cannot be predicted by computational logarithms. As the studies typically address only one or a few number of microRNAs in the experiments, it remains a challenge to design pre-clinical studies based on computational predictions (Lai, 2002; S. C. Li et al., 2010).

Regarding the above mentioned, and that understanding how microRNAs effectively regulate BDNF actions provide basis for the development of potential therapies against neurodegenerative conditions; we have collected all the available data on the post-transcriptional regulation of BDNF by microRNAs evidenced in experimental studies, and provided a synthesis of the regulatory mechanisms currently demonstrated.

Methods

In order to retire all the scientific publications possibly reporting data from the analysis of microRNAs and BDNF expression in a same biological system, a systematic search was conducted on PubMed.gov using the following combination of terms: ["BDNF" AND "MicroRNA"] OR ["brain-derived neurotrophic factor" AND "MicroRNA"]. All the available publications were retrieved and screened by abstract. Papers published without open-access were requested from the authors via email or ResearchGate. Studies containing data from BDNF and microRNA analyses *in vivo* or *in vitro* were considered for inclusion. The studies reporting data of microRNAs that did not influence on BDNF regulation, Reviews, articles not written in English, high throughput profiles and computational predictor studies, as well as those not made available by the authors were excluded from discussion during full text assessment. The last search update, performed in September 1th 2023, launched 314 papers published from 2006 to 2023 indexed in PubMed (see Figure 1). The studies selection was performed using the software Mendeley 1.19.8.

Two-hundred and ninety-seven articles were sought for retrieval according to the inclusion criteria of containing data from BDNF and microRNA analyses, after duplicates removal. Two hundred and sixty-one papers were assessed by full text. A total of 172 were found to include the analyses of BDNF and diverse microRNAs and were included in the qualitative synthesis, after exclusion criteria (Figure 1). A list of the studies and microRNAs involved in BDNF regulation was displayed in Table 1.

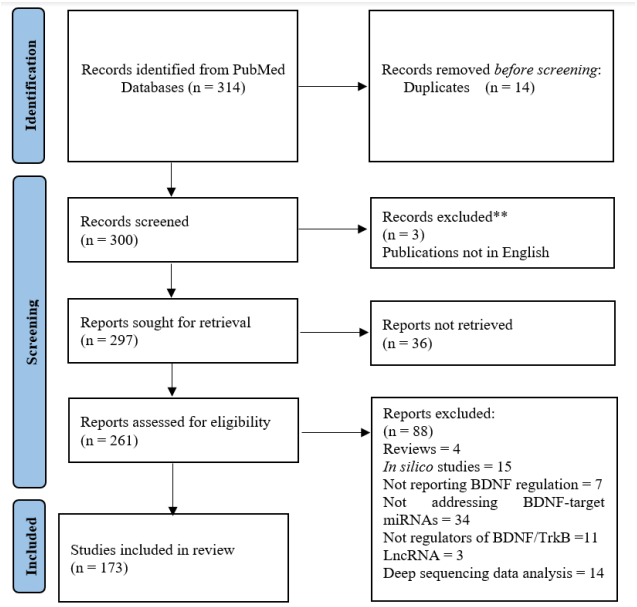

Figure 1. Search flow chart.

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Table 1. MicroRNAs that participate in BDNF regulation.

1	Schratt, G. M., et al. (2006). https://doi.org/10.1038/nature04367	miR-134
2	Klein, M. E., et al. (2007). https://doi.org/10.1038/nn2010	miR132
3	Mellios, N., et al. (2008). https://doi.org/10.1093/hmg/ddn201	miR-30a-5p miR-195
4	Mellios, N., et al. (2009). https://doi.org/10.1016/j.biopsych.2008.11.019	miR-195
5	Chandrasekar, V., & Dreyer, J. L. (2009). https://doi.org/10.1016/j.mcn.2009.08.009	miR-124
6	Im, H.-I., et al. (2010). https://doi.org/10.1038/nn.2615	MeCP2
7	Gao J. amd Wang, et al. (2010). https://doi.org/10.1038/NATURE09271	miR-134
8	Kawashima, H., et al. (2010). https://doi.org/10.1016/j.neuroscience.2009.11.057	miR-132
9	Han, L., et al. (2011). https://doi.org/10.1186/1756-6606-4-40	miR-134
10	Radzikinas, K., et al. (2011). https://doi.org/10.1523/JNEUROSCI.2745-11.2011	miR-206
11	Angelucci, F., et al. (2011). https://doi.org/10.1159/000322528	miR30a-5p
12	Caputo, V., et al. (2011). https://doi.org/10.1371/journal.pone.0028656	miR-26a1/2 miR-26b
13	Bai, M., et al. (2012). https://doi.org/10.1371/journal.pone.0046921	miR-16
14	Lee, S. T., et al. (2012). https://doi.org/10.1002/ana.23588	miR-260
15	Imam, J. S., et al. (2012). https://doi.org/10.1371/journal.pone.0052397	miR-204
16	Chen-Plotkin, A. S., et al. (2012). https://doi.org/10.1523/JNEUROSCI.0521-12.2012	miR-132
17	Wibrand, K., et al. (2012). https://doi.org/10.1371/journal.pone.0041688	miR-132
18	Miura, P., et al. (2012). https://doi.org/10.1111/j.1471-4159.2011.07583.x	miR-206
19	Bahi, A., & Dreyer, J.-L. (2013). https://doi.org/10.1111/ejn.12228	miR124a
20	Hutchison, E. R., et al. (2013). https://doi.org/10.1002/glia.22483	McCP2
21	SUN, Y.-X., et al. (2013). https://doi.org/10.3892/or.2013.2731	miR-16

 doi:10.20944/preprints202404.0225.v1

22	Li, Y.-J., et al. (2013). https://doi.org/10.1371/journal.pone.0063648	miR-182
23	Kynast, K. L., et al. (2013). https://doi.org/10.1016/j.pain.2012.11.010	miRNA-124a
24	Croce, N., et al. (2013). https://doi.org/10.1007/s11010-013-1567-0	NPY
25	Ryan, K. M., et al. (2013). https://doi.org/10.1016/j.neulet.2013.05.035	miR-212
26	Nagpal, N., et al. (2013). https://doi.org/10.1093/carcin/bgt107	miR-191
27	Mojtahedi, S., et al. (2013). https://doi.org/10.1002/cbin.10022	miR-124
28	Tapocik, J. D., et al. (2014). https://doi.org/10.1523/JNEUROSCI.0445-14.2014	miR-206
29	Lin, C. R., et al. (2014). https://doi.org/10.1111/ejn.12522	miR-183
30	Tian, N., et al. (2014). https://doi.org/10.1007/s12264-013-1419-7	miR-206
31	Bahi, A., et al. (2014). https://doi.org/10.1016/j.psyneuen.2014.04.009	miR124a
32	Marler, K. J., et al. (2014). https://doi.org/10.1523/JNEUROSCI.1910-13.2014	miRNA-132
33	Yang, X., et al. (2014). https://doi.org/10.1007/s12017-014-8312-z	miR-206
34	Yi, L. T., et al. (2014). https://doi.org/10.1503/jpn.130169	miR-132
35	Giannotti, G., et al. (2014). https://doi.org/10.1017/S1461145713001454	miR124 miR132
36	Varendi, K., et al. (2014). https://doi.org/10.1007/s00018-014-1628-x	miR-1/206 miR-10
37	Zhang, J., et al. (2014). https://doi.org/10.3760/cma.j.issn.0366-6999.20131683	miR- 34a
38	Cho, K. J., et al. (2015). https://doi.org/10.1016/j.mcn.2015.07.004	miR-Let-7a
39	Li, H., et al. (2015). https://doi.org/10.3892/mmr.2015.3736	miR-183/96/182
40	Ma, J. C., et al. (2015). https://doi.org/10.1016/j.neuroscience.2015.04.061	miR-1
41	Yang, G., et al. (2015). https://doi.org/10.3892/mmr.2015.3531	miR-29c
42	Neumann, E., et al. (2015). https://doi.org/10.1186/s12990-015-0045-y	miR-1

 doi:10.20944/preprints202404.0225.v1

43	Li, W., et al. (2015). https://doi.org/10.1155/2015/302653	miR-22
44	Xiang, L., et al. (2015). https://doi.org/10.1016/j.brainres.2015.06.046	miR-132 miR-132
45	Yan, H., et al. (2015). https://doi.org/10.1097/IGC.0000000000000456	miR-204
46	Mu, Y., et al. (2015). https://doi.org/10.3892/mmr.2015.4456	miR-206-3p
47	Li, M., et al. (2015). https://doi.org/10.1002/path.4484	miRNA-134 miR-132
48	Liu, Z., et al. (2015). https://doi.org/10.1159/000430356	miR-937
49	Su, M., et al. (2015). https://doi.org/10.3892/mmr.2015.4104	MeCP2
50	Hernandez-Rapp, J., et al. (2015). https://doi.org/10.1016/j.bbr.2015.03.032	miR-132/212
51	Huang, W., et al. (2015). https://doi.org/10.1007/s12031-015-0500-2	miR-134
52	Oikawa, H., et al. (2015). http://doi.org/10.1016/j.neuint.2015.10.010	miR-124
53	Jiang, Y., & Zhu, J. (2015). http://www.ncbi.nlm.nih.gov/pubmed/25755749	miR-10B
54	Shao, Y., et al. (2015). https://doi.org/10.1007/s12031-015-0522-9	miR-134
55	Gao, Y., et al. (2015). https://doi.org/10.1002/stem.1950	miR-15a+
56	Darcq, E., et al. (2015). https://doi.org/10.1038/mp.2014.120	miR-30a-5p
57	Long, J., et al. (2016). https://doi.org/10.1007/s13277-015-4427-6	MiR-15a-5p
58	Hu, X. M., et al. (2016). https://doi.org/10.1177/1744806916666283	miR-219
59	Li, Y., et al. (2016). https://doi.org/10.1016/j.pnpbp.2015.09.004	miR-182
60	Peng, J. Y., et al. (2016). https://doi.org/10.1016/j.domaniend.2015.09.005	miR-10b
61	Yi, S., et al. (2016). https://doi.org/10.1038/srep29121	miR-1
62	Bahi, A. (2016). https://doi.org/10.1016/j.bbr.2016.05.033	miR124a
63	Xia, H., Li, Y., & Lv, X. (2016). https://doi.org/10.3892/ijo.2016.3628	miR-107

 doi:10.20944/preprints202404.0225.v1

64	Neumann, E., et al. (2016). https://doi.org/10.1016/j.mcn.2016.06.003	miR-1
65	Kumari, A., et al. (2016). https://doi.org/10.1016/j.physbeh.2016.02.032	miRNA-132 and miRNA-134
66	Liang, Y., et al. (2016). https://doi.org/10.1177/1744806916641679	miRNA-212/132
67	Jiang, B., et al. (2016). https://doi.org/10.3892/mmr.2016.5810	miR-9
68	Hang, P., et al. (2016) https://doi.org/10.7150/ijbs.15071	miRNA-195
69	Li, W., et al. (2016). https://doi.org/10.5582/bst.2016.01127	miR-613
70	Jimenez-Gonzalez, A., et al. (2016). https://doi.org/10.1016/j.bbagen.2016.03.001	miR-212 and miR-132
71	Aili, A., Chen, Y., & Zhang, H. (2016). https://doi.org/10.3892/mmr.2015.4506	miR-10b
72	Zeng, L. L., et al. (2016). https://doi.org/10.1111/cns.12589	MiR-210
73	Xiang, L., et al. (2016). https://doi.org/10.1016/j.brainres.2016.02.045	MiR-204
74	Cui, M., et al. (2017). https://doi.org/10.1016/j.bbadis.2017.06.021	miR-34a-5p
75	Thomas, K. T., et al. (2017). https://doi.org/10.1016/j.celrep.2017.06.038	miR-137
76	Mendoza-Viveros, L., et al. (2017). https://doi.org/10.1016/j.celrep.2017.03.057	miR-132/212
77	Xie, B., et al. (2017). https://doi.org/10.3233/JAD-160468	miR-206
78	Wang, P., et al. (2017). https://doi.org/10.18632/oncotarget.13747	miR-497
79	Gao, B., et al. (2017). https://doi.org/10.1002/jgm.2932	miR-107
80	Tu, Z., et al. (2017). https://doi.org/10.1016/j.biopha.2017.05.016	miR-140
81	Song, D., ett al. (2017). https://doi.org/10.3892/mmr.2017.7396	miR-382
82	Lin, C. Y., et al. (2017). https://doi.org/10.1038/cddis.2017.354	miR-624-3p
83	Zhao, Y., et al. (2017). https://doi.org/10.1016/j.brainres.2017.05.020	miR-101
84	Zhang, K., et al. (2017). https://doi.org/10.1042/BSR20170755	miR-211
85	Bahi, A. (2017).	miR124a

 doi:10.20944/preprints202404.0225.v1

	https://doi.org/10.1016/j.bbr.2017.03.010	
86	Xu, A. J., et al. (2017). https://doi.org/10.3892/mmr.2017.7167	miR-744
87	Sun, W., et al. (2017). https://doi.org/10.1016/j.neulet.2016.12.047	miR-206
88	Wang, S. S., et al. (2017). https://doi.org/10.1016/j.pnpbp.2017.07.024	miR-124
89	(Wang et al., 2017) https://doi.org/10.3892/mmr.2017.8282	miR-103
90	Huang, W., et al. (2017). https://doi.org/10.1007/s12031-017-0907-z	MiR-134
91	Ji, M., et al. (2017). https://doi.org/10.3892/mmr.2017.7626	miR-705
92	Fu et al., (2017) http://dx.doi.org/10.1038/s41598-017-01261-x	miR-125b-5p
93	Lian, N., et al. (2018). https://doi.org/10.1080/15384101.2018.1556060	miR-221
94	Duan, W., et al. (2018). https://doi.org/10.3892/ijmm.2018.3711	miR-155
95	Yi, L. T., et al. (2018). https://doi.org/10.1177/0269881118758304	miR-124
96	Nguyen, T., et al. (2018). https://doi.org/10.1073/pnas.1803384115	let-7i
97	Cheng, F., et al. (2018). https://doi.org/10.1016/j.micpath.2018.04.060	miR-107
98	Fang, Y., et al. (2018). https://doi.org/10.1016/j.jad.2017.11.090	miR-124
99	Zhang, S., et al. (2018). https://doi.org/10.1016/j.neulet.2017.10.014	miR-210-3p
100	Xing, Q., et al. (2018). https://doi.org/10.1055/a-0658-2095	miR-206
101	Li, X. J. (2018). https://doi.org/10.1177/1479164117749382	miR-497
102	Lu, Y., et al. (2018). https://doi.org/10.1007/s10571-018-0599-0	miR-155
103	Miao, Z., et al. (2018). https://doi.org/10.1007/s12035-016-0378-1	miR-206-3p
104	Descamps, B., et al. (2018). https://doi.org/10.1161/ATVBAHA.118.311400	miR-214
105	Lv, M., Yet al. (2018). https://doi.org/10.1002/mnfr.201800621	miR-26a miR-125b miR-132
106	Ge, Q. Di, et al. (2018). https://doi.org/10.1016/j.etap.2018.08.011	miR-132 miR-204

 doi:10.20944/preprints202404.0225.v1

107	Shen, J., et al. (2018). https://doi.org/10.1016/j.bbr.2018.04.050	miR-134
108	Wu, B. W., et al. (2018). https://doi.org/10.1002/jcp.26328	miR-10a
109	Ma, J. C., et al. (2018). https://doi.org/10.1159/000494657	miR-1
110	Zhang, X. yu, et al. (2018). https://doi.org/10.1016/j.lfs.2018.09.002	miR-10a
111	Gao, L., et al. (2018). https://doi.org/10.4149/neo_2018_161128N594	MiR-1-3p
112	Zhang, J., et al. (2018). https://doi.org/10.1007/s11064-018-2475-1	miR-322
113	Jiang, J. D., et al. (2019). https://doi.org/10.1002/iub.1911	miR-107
114	Yang, W., et al. (2019). https://doi.org/10.1002/jcp.28862	miR-124
115	Shrestha, S., et al. (2019). https://doi.org/10.1002/2211-5463.12581	miRNA-206
116	Miao, Z., et al. (2019). https://doi.org/10.1016/j.neuropharm.2019.03.032	miR-30a
117	Song, Y., et al. (2019). https://doi.org/10.3892/mmr.2019.10424	miR-584
118	Sun, Z., et al. (2019). https://doi.org/10.1002/jcp.26928	miR-497
119	Mohammadipoor-Ghasemabad, L., et al. (2019). https://doi.org/10.1016/j.neuroscience.2019.06.037	miR-191a
120	Hung, Y. Y., et al. (2019). https://doi.org/10.3390/cells8091021	miR-204-5p
121	Li, B. B., et al. (2019). https://doi.org/10.1016/j.chemosphere.2019.05.064	miR-7
122	Ma, R.,et al. (2019). https://doi.org/10.1016/j.bbrc.2019.08.046	miR-496
123	Shen, J., et al. (2019). https://doi.org/10.1016/j.jad.2019.01.031	miR-134
124	Solomon, M. G., et al. (2019). https://doi.org/10.1016/j.neuroscience.2019.02.012	miR-206
125	Zhao, X., et al. (2019). https://doi.org/10.1016/j.ejphar.2018.11.035	miR-375
126	Panta, A., et al. (2019). https://doi.org/10.1016/j.bbi.2019.01.003	miR-363-3p
127	Zhao, H., et al. (2019). https://doi.org/10.1016/j.neuroscience.2019.07.051	miR-206

 doi:10.20944/preprints202404.0225.v1

128	Xie, W., et al. (2020). https://doi.org/10.1007/s11064-020-03013-2	miR-185
129	Deng, C., et al. (2020). https://doi.org/10.1007/s11064-019-02910-5	miR-494-3p
130	Hu, J. J., et al. (2020). https://doi.org/10.1002/kjm2.12136	miR-15a
131	Liu, X., et al. (2020). https://doi.org/10.1080/15384101.2019.1710916	MiR-192-5p
132	Zhang, T., et al. (2020). https://doi.org/10.1016/j.neulet.2019.134562	miR-10a-5p
133	Yang, W., et al. (2020). https://doi.org/10.2174/1567202617666200319141755	miR-124
134	Wu, G., et al. (2020). https://doi.org/10.1016/j.yexcr.2020.111937	miR-129-5p
135	Liu, H., et al. (2020). https://doi.org/10.14670/HH-18-266	miR-204-5p
136	Misiorek, J. O., et al. (2020). https://doi.org/10.1007/s12035-020-01899-1	miR-10a-5p
137	Wang, F., et al. (2020). https://doi.org/10.3892/mmr.2020.11065	mir-210
138	Wang, L., et al. (2020). https://doi.org/10.1007/s11010-020-03726-6	miR-10b-5p
139	Gao, L., et al. (2020). https://doi.org/10.1093/JNEN/NLAA069	miR-103-3p
140	Giordano, M., et al. (2020). https://doi.org/10.3390/ijms21207615	miR-195-5p
141	Xu, H., et al. (2020). https://doi.org/10.12659/MSM.920855	miR-216a-5p
142	Pejhan et al., (2020) https://doi.org/10.3389/fcell.2020.00763	miR-132
143	Lin, B., et al. (2021). https://doi.org/10.18632/aging.103640	miR-155
144	Niu, Y., et al. (2021). https://doi.org/10.1186/s10020-020-00258-z	miR-186
145	Zhang, X., et al. (2021). https://doi.org/10.1016/j.bbr.2020.113087	miR-432
146	Huan, Z., et al. (2021). https://doi.org/10.1007/s11064-021-03234-z	miR-155
147	Zhao, P., et al. (2021). https://doi.org/10.1007/s11255-021-02853-3	miR-365
148	Ke, X., et al. (2021). https://doi.org/10.1159/000515750	miR-10b-5p

 doi:10.20944/preprints202404.0225.v1

149	Xu, Y., et al. (2021). https://doi.org/10.1080/21655979.2021.1918991	miR-191-5p
150	Pan, S., et al. (2021). https://doi.org/10.1038/s41398-021-01240-x	MiR-195
151	Li, H., et al. (2021). https://doi.org/10.1080/15376516.2021.1886211	miR-191
152	Tang, Y., et al. (2021). https://doi.org/10.1371/journal.pone.0257280	miR-155
153	Li, X., et al. (2021). https://doi.org/10.5114/fn.2021.105132	miR-1b
154	Peng, D., et al. (2022). https://doi.org/10.7150/thno.70951	miR-206-3p
155	Wu, Y., et al. (2021). https://doi.org/10.4103/0028-3886.333459	miR-191-5p
156	Guan, W., et al. (2021). https://doi.org/10.1016/j.phrs.2021.105932	miR-206-3p
157	Zhang, Q., et al. (2021). https://doi.org/10.3389/fendo.2021.637384	miR-103a-3p miR-10a-5p
158	Ehinger, Y., et al. (2021). https://doi.org/10.1111/adb.12890	miR30a-5p miR-195-5p miR191-5p miR206-3p
159	Fang, F., et al. (2022). https://doi.org/10.1186/s13019-022-01802-0	miR-182-5p
160	Su, B., et al. (2022). https://doi.org/10.1080/21655979.2022.2059937	miR-139-5p
161	Yongguang, L., et al. (2022). https://doi.org/10.1186/s12906-021-03483-z	miR-497
162	Tu, W., et al. (2022). https://doi.org/10.1155/2022/1489841	miR-206-3p
163	Gao, J., et al. (2022). https://doi.org/10.1080/21655979.2022.2067293	miR-155-5p
164	Zhai, Y., et al. (2022). https://doi.org/10.1002/kjm2.12486	miR-210
165	Yu, H. C., et al. (2022). https://doi.org/10.3390/ijms23010570	miR-3168
166	Kang, E. M., et al. (2022). https://doi.org/10.1111/cns.13845	miR- 124-3p
167	Li, C., et al. (2022). https://doi.org/10.3892/mmr.2021.12577	mir-182-5p
168	Deng, L., et al. (2022). https://doi.org/10.1186/s13018-022-03315-x	miR-210-3p
169	Ding, J., Jiang, C., Yang, L., & Wang, X. (2022). https://doi.org/10.14715/CMB/2022.68.1.10	miR-1-3p
170	Ma, L., et al. (2022).	miR-132-5p

 doi:10.20944/preprints202404.0225.v1

	https://doi.org/10.1038/s41398-022-02192-6	
171	Asadi, M. R., et al. (2022). https://doi.org/10.1186/s12888-022-04442-9	miR-16
172	Wang, L., et al. (2022). https://doi.org/10.1016/j.brainresbull.2022.03.002	miR-551b-5p
173	Zhang, Z., et al. (2022). https://doi.org/10.1016/j.bbrc.2022.05.038	miR-382 miR-182

Results

Discussion

BDNF by microRNAs

A great number of microRNAs are able to target and influence BDNF activity (Figure 2). The post-transcriptional regulation of BDNF can influence on BDNF synthesis and activity in a non-specific manner throughout tissues. Moreover, in addition to the ability to target and degrade the transcripts of BDNF mRNA in a 'direct regulation', microRNAs can affect the activity of BDNF (either positively or negatively) via regulation of other factors, here referred as 'indirect regulation'. Great part of research identifying BDNF-target microRNAs regard to investigations on the oncogenicity of BDNF/TrkB signal transduction in tumor cell growth and metastasis (Y. Li et al., 2023; Ni & Zhang, 2020). A list of microRNAs found to degrade BDNF mRNA transcripts in oncology research follows: miR-10a, miR-22, miR-204, miR-107, miR-382, miR-496, miR-497, miR-584, miR-744, miR-26a-1 and miR-26a-2 subtypes (Caputo et al., 2011; Cheng et al., 2018; B. Gao et al., 2017; L. Gao et al., 2018; Imam et al., 2012; J. D. Jiang et al., 2019; R. Li et al., 2018; Wu Li et al., 2015; Long et al., 2016; R. Ma et al., 2019; J. Y. Peng et al., 2016; D. Song et al., 2017; Y. Song et al., 2019; Z. Sun et al., 2019; P. Wang et al., 2017; Xia et al., 2016; Xiang et al., 2016; A. J. Xu et al., 2017; Yan et al., 2015; Xiao yu Zhang et al., 2018). The evidences that miR-206 is able to suppress BDNF synthesis in diverse tissues such as the cardiac muscles, the skeletal muscles and the endothelial tissue elucidate a role for microRNAs in a tissue-tissue communication, although their actions might be locally regulated (Guan et al., 2021; S. T. Lee et al., 2012; Mu et al., 2015; D. Peng et al., 2022; Solomon et al., 2019; W. Sun et al., 2017; Tapocik et al., 2014; Tian et al., 2014; W. Tu et al., 2022; M. Wang et al., 2018; Xie et al., 2017; Xing et al., 2018; X. Yang et al., 2014; H. Zhao et al., 2019).

Some microRNAs can be are exported from cells by membrane-derived vesicles, lipoproteins, and other ribonucleoprotein complexes and travel through the blood stream reaching recipient cells in distant tissues (Boon & Vickers, 2013), providing a communication between disparate cell types and diverse biological mechanisms and homeostatic pathways. Our data collection reports a number of microRNAs whose circulating levels are increased in inflammatory conditions and that demonstrably suppress BDNF synthesis in the CNS, namely: miR-1, miR-128, miR-182-5p, miR-195-5p and miR-451a (F. Fang et al., 2022; Jian Gao et al., 2022; Giordano et al., 2020; J. C. Ma et al., 2015; Misiorek et al., 2020). Among those circulating microRNAs which suppress BDNF synthesis, some were found involved in the physiopathology of neuropsychiatric disorders and disease such as anxiety/depression – miR-182, miR-206-3p, miR-1-3p, MiR-16, miR-124, miR-432 and miR-182 (Bai et al., 2012; Ding et al., 2022; Y. Fang et al., 2018; Y. J. Li et al., 2013; Miao et al., 2018; Y. X. Sun et al., 2013; Xiaonan Zhang et al., 2021; Z. Zhang et al., 2022), Schizophrenia - miR-16, miR-195 and miR-30a-5p (Asadi et al., 2022; Mellios et al., 2008, 2009; Pan et al., 2021), Parkinson's disease - miR-494-3p (C. Deng et al., 2020) and Dementia - miR-10a, miR-34a-5p, miR-204 and miR-613 (Cui et al., 2017; Ge et al., 2018; Giannotti et al., 2014; Lambert et al., 2003; Wei Li et al., 2016; Ji Chao Ma et al., 2018; Ryan et al., 2013; B. W. Wu et al., 2018). Together, those findings suggest a mechanistic *crosstalk* driven by microRNAs between inflammation in peripheral systems and neurodegenerative processes.

MicroRNAs play crucial roles in immunoinflammatory reactions. In normal conditions, the CNS parenchyma is not exposed to peripheral immune cells or robust inflammatory responses and

 doi:10.20944/preprints202404.0225.v1

microglia and astrocytes remain quiescent. However, upon stress, astrocytes and microglia transiently activate and produce chemokines and cytokines, and other small molecule messengers (prostaglandins, nitric oxide, reactive oxygen species - ROS) which contribute to the inflammatory response and subsequent restoration of CNS homeostasis (Jingdan Zhang et al., 2023). The study by (Kynast et al., 2013) identified that miR-124 is constitutively expressed in neuron of the dorsal horn in spinal cord, where its elevation is associated with a decrease in BDNF levels. While a decrease in miR-124 levels lead elevation in MeCP2 and BDNF expression levels. From a different perspective, the studies by (Duclot & Kabbaj, 2017; Wenqian Yang et al., 2019) demonstrated that miR-124 is able to attenuate an acute increase in pro-inflammatory factors in the CNS, by suppressing the early growth response 1 (EGR1) and preventing a decline in BDNF expression. Conversely, (Yu et al., 2022) showed that BDNF administration increased the expression levels of miR-3168, and suppressed the secretion of interleukin (IL)-1β, TNF-α, and IL-6 in the activated macrophage.

Another mechanism by which microRNAs indirectly modulate BDNF synthesis in inflammatory conditions involve the Let-7 miRNA family (Roush & Slack, 2008), which include let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98 and miR-202 (Y. Ma et al., 2021). Dysregulation of let-7 leads to a less differentiated cellular state and cell-based diseases such as cancer. Cho and colleagues (2015) investigation in neural tissue reported that let-7a levels increase in microglia following the accumulation of ROS and pro-inflammatory cytokines. The data indicated that let-7a participates in reducing nitrite production while increasing the levels of inducible NO synthase and IL-6. Anti-inflammatory events that accompanied an upregulation in BDNF expression levels. Alternatively, (Nguyen et al., 2018) detected that miR-let-7i suppresses the synthesis of progesterone receptor membrane component 1, reducing progesterone-inducible release of BDNF by astrocytes. Such reduction has a negative effect on neuronal tissue recovery. These findings show that Let-7 members might exert specific roles that positively or negatively affect BDNF function in CNS parenchyma.

Although the regulation of a protein function by microRNAs mostly always depend on their nucleotide sequence to target mRNA transcripts present in a same micro environment; i*n silico* predictions of BDNF target microRNAs are not always confirmed in biological systems. Meanwhile, some experiments have pointed out that microRNA targeting of BDNF mRNA is selectively guided by their prime untranslated region (3′-UTR) (Caputo et al., 2011; Shrestha et al., 2019; Varendi et al., 2014; Jun Zhang et al., 2018). Having noted the presence of two variants of 3′ UTR regions in the mRNA transcripts of BDNF, which exert an influence on their cellular trafficking/localization (Lekk et al., 2023), the mechanistic regulation of BDNF by microRNA within a cell might as well occurs in a local specificity manner, a least in cells that express the two BDNF mRNA 3′ UTR isoforms.

Neuroplasticity and BDNF Regulation by microRNAs

The expression of BDNF is present in progenitor cells from the early embryonic phase and in neural tissue throughout the whole lifespan. It participation in essential processes such as dendritogenesis, axonal innervation and synaptogenesis, neuronal growth and survival guaranties the maintenance and proper functioning of the neuronal tissue (Barde et al., 1987; Citri & Malenka, 2008; Robinson, 1996).

A growing number of microRNAs have been identified as direct regulators of BDNF in the neural tissue. Here, we list some of the microRNAs that target and degrade BDNF mRNA transcripts and modulate BDNF actions in processes such as neuronal cell growth, differentiation and proliferation: miR-1, miR-1b, miR-1-3p, miR-10a, miR-10b, miR-10a-5p, miR-15a, miR-16, miR-26a, miR-34a, miR-103, miR-125b, miR-125b-5p, miR-30a-5p, miR-34a-5p, miR-140, miR-139-5p, miR-155, miR-191, miR-181, miR-186, miR-191, miR-191-5p, miR-191a-5p, miR-204-5p, miR-206, miR-210, miR-210-3p miR-211, miR-216a-5p, miR-219, miR-636-3p, miR-365, miR-375, miR-551b-5p, miR-937, miR-497 and the miR-497a subtypes (Aili et al., 2016; Angelucci et al., 2011; Burckhardt et al., 2019; Croce et al., 2013; Darcq et al., 2015; L. Deng et al., 2022; Duan et al., 2018; Ehinger et al., 2021; Fu et al., 2017; Lin Gao et al., 2020; J. J. Hu et al., 2020; X. M. Hu et al., 2016; Huan et al., 2021; Hung et al., 2019; Hutchison et al., 2013; Y. Jiang & Zhu, 2015; Ke et al., 2021; Hongxia Li et al., 2021; Xiaojie Li et al., 2021; Xiu-juan Li, 2018; S. P. Liang et al., 2019; B. Lin et al., 2021; H. Liu et al., 2020; X. Liu et al., 2020;

 doi:10.20944/preprints202404.0225.v1

Zhen Liu et al., 2015; Lu et al., 2018; Lv et al., 2018; Miao et al., 2019; Mohammadipoor-Ghasemabad et al., 2019; Nagpal et al., 2013; Neumann et al., 2015, 2016; Niu et al., 2021; Panta et al., 2019; Scheen et al., 2015; B. Su et al., 2022; Tang et al., 2021; Z. Tu et al., 2017; F. Wang et al., 2020; Li Wang et al., 2020; Linxiao Wang et al., 2022; P. Wang et al., 2017; G. Wu et al., 2020; Y. Wu et al., 2021; H. Xu et al., 2020; W. Xu et al., 2022; Y. Xu et al., 2021; S. Yi et al., 2016; Yongguang et al., 2022; Zeng et al., 2016; Zhai et al., 2022; Jing Zhang et al., 2014; Jun Zhang et al., 2018; K. Zhang et al., 2017; T. Zhang et al., 2020; Xiao yu Zhang et al., 2018; P. Zhao et al., 2021; X. Zhao et al., 2019).

Some studies showed that Sonic hedgehog (Shh) is able to relief the suppression exerted by miR-206 on BDNF synthesis, which led to an enhancement in BDNF-TrkB signaling during the processes of differentiation and innervation in muscle cells (Miura et al., 2012; Radzikinas et al., 2011). Shh is a key signaling molecule in the embryonic morphogenesis and organization of nervous system. Its signaling via receptor Patched mediated Smoothened receptor complex is putative to the development of neural tube; whereas, abnormal activation of Shh signaling implicates in various types of cancers (Odent et al., 1999). This indirect and positive effect of Shh on BDNF activity seem to be involved in a complex and phasic destabilization of cell homeostasis during differentiation in mesenchymal cells.

BDNF binding to TrkB receptors at neuronal cells surface lead to the dimerization and transphosphorylation of a critical regulator of actin dynamics in the axons and dendrites named LIM Domain Kinase 1 (LIMK1). This occurs independently of TrkB kinase activity. The LIMK1 mRNA transcript is a target for miR-134 in the axon and dendrite cell compartments, and is able to annul BDNF/TrkB-induced protein synthesis during the synaptic activity, whenever TrkB activation is not sufficient to surpass miR-134 suppression on LIMK1. This suggest that miR-134 actively participates in competitive synapses formation; and establishes a role for this microRNA in the fine tune regulation of neuroplasticity processes (Dong et al., 2012; Jun Gao et al., 2010; Han et al., 2011; Kim et al., 2019; Kumari et al., 2016; M. Li et al., 2015; Schratt et al., 2006).

Several microRNAs were found to target different components of BDNF-TrkB signaling intracellular cascades, consequently decreasing the activity of cAMP response element binding (CREB) protein, leading to a decrease in *BDNF* gene expression. The investigation by (Thomas et al., 2017) identified that miR-137 regulates the levels of various proteins within the PI3K-Akt-mTOR pathway in neurons, namely: p55g, PTEN, Akt2, GSK3b, mTOR, and rictor. And this negatively affects BDNF- induced dendritic outgrowth. In addition, the miR-221, miR-383 and miR-199a-5p were shown to suppress the synthesis of Wnt2, which is a glycoprotein with essential roles in the embryonic development and dendrite development (Wayman et al., 2006). The neuronal activity enhances CREB-dependent transcription of Wnt2, which in turn, stimulates dendritic arborization. Both Wnt2 and BDNF are CREB-responsive genes and so Wn2t suppression results in a decrease in BDNF expression possibly via a Wnt2/CREB/BDNF axis (Lian et al., 2018; S. Liu et al., 2021; Zheng Liu et al., 2021). Additionally, some microRNAs were reported as negatively correlated with the levels of BDNF in studies, i.e. miR-183/96 (Hongyang Li et al., 2015; C. R. Lin et al., 2014), miR-134 (Huang et al., 2017; Shen et al., 2018, 2019), and miR-182-5p (F. Fang et al., 2022; C. Li et al., 2022).

 doi:10.20944/preprints202404.0225.v1

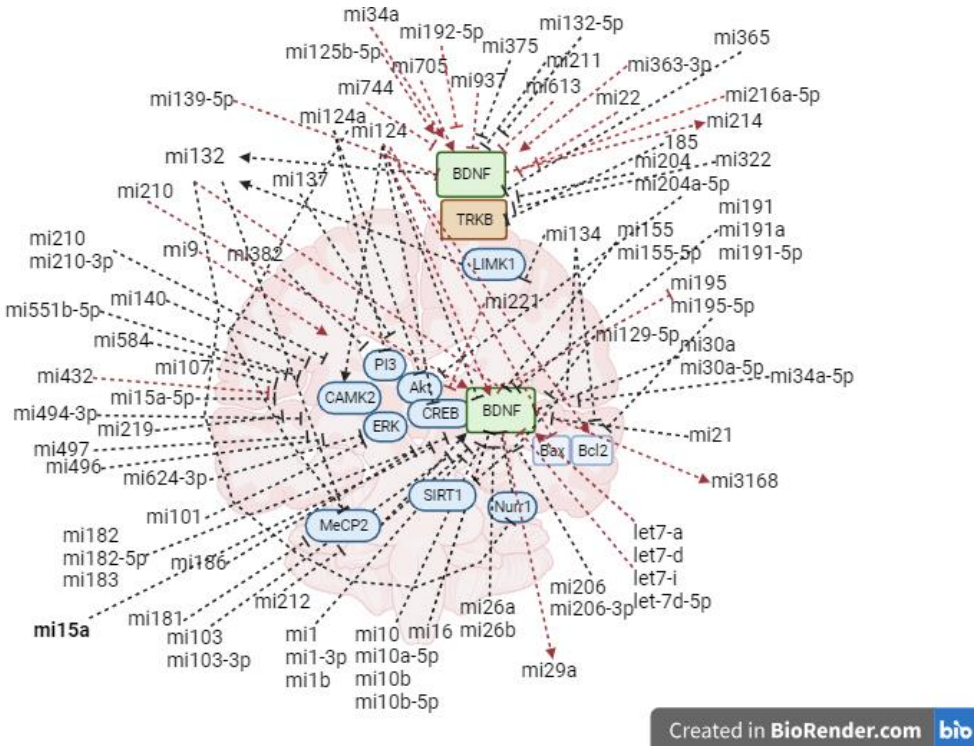

Figure 2. BDNF regulation by microRNAs. Black lines; positive (arrows) and negative (cut lines) regulation predictions confirmed in tissue samples, Red lines: positive (arrows) and negative (cut lines) associations between microRNA and BDNF levels.

Cell Metabolism and BDNF Regulation by microRNAs

The post-transcriptional regulation of proteins elicits compensatory mechanisms to maintain transcriptional activity of essential proteins involved in cell energy homeostasis. The integrative regulation of a number of proteins in the core of cell metabolism homeostasis affects *BDNF* gene expression by various manners, including it self-regulation via autocrine and/or paracrine TrkB signaling. BDNF/TrkB activation leads to the activation of several small G proteins in addition to the pathways regulated by mitogen-activated protein kinase (MAPK), PI 3-kinase (PI-3K), and phospholipase-Cγ (PLCγ) (Numakawa et al., 2010). Meanwhile, as miR-101 suppresses MAPK phosphatases 1 (which dephosphorylates p38, JNK and ERK), it has a positive effect on ERK phosphorylation and the downstream activation of *BDNF* expression in cortical neurons (Y. Zhao et al., 2017).

The activity of AMP-activated protein kinase (AMPK) and CREB represent the axis of cell energy metabolism. A compensatory increase in CREB activity following a decrease in the concentrations of BDNF and methyl CpG binding protein 2 (MeCP2) was evidenced in the brain of 132/212 KO mice (Hernandez-Rapp et al., 2015; Klein et al., 2007). While MeCP2 is a nuclear protein that may function as both a transcriptional activator or repressor, it works as a stabilizer of BDNF expression patterns and cell homeostasis (Buist et al., 2021; Pejhan et al., 2020; Vuu et al., 2023). Another compensatory effect is seen for BDNF in dendritogenesis when inhibition of miR-15a, and the consequent relief of BDNF supression, can rescue dendritic maturation deficits in MeCP2-deficient neurons (Y. Gao et al., 2015). Further, upregulation in *BDNF* gene expression accompanies an increase in the expression of miR-132/212 cluster; both of which target and suppress MeCP2 mRNA translation. Suppression of miR-132 and miR-212 on MeCP2 relieves its repression on *BDNF* expression. By this manner, the expression of BDNF and miR-132 and miR-212 represent a self-regulatory homeostatic mechanism that involves the nuclear protein MeCP2 at the core of cell metabolism (Chen-Plotkin et al., 2012; Im et al., 2010; Jimenez-Gonzalez et al., 2016; Kawashima et al., 2010; Klein et al., 2007; Y. Liang et al.,

 doi:10.20944/preprints202404.0225.v1

2016; Marler et al., 2014; Mendoza-Viveros et al., 2017; M. Su et al., 2015; Wibrand et al., 2012; L. T. Yi et al., 2014).

The enzymatic activity of the histone deacetylase Sirtuin 1 (SIRT1) in the nicotinamide adenine dinucleotide (NAD)-dependent deacetylation of histones is crucial to protect cells from oxidative stressors. SIRT1 activates the expression of mitochondrial DNA genes related to mitochondrial biogenesis, ATP generation and cell proliferation. It was detected in experiments that SIRT1 is able to inhibit miR-134 expression by directly binding to its inhibitory elements. Whereas, SIRT1 deficiency and high levels of miR-134 result in a downregulation of CREB and *BDNF* expression, and a negative effect on neuronal survival/plasticity. Another indirect mechanism by which miR-134 negatively affects BDNF function in the core of cell metabolism (Jun Gao et al., 2010; Huang et al., 2015, 2017; Shao et al., 2015; Shen et al., 2019). Finally, the study by (Oikawa et al., 2015) showed that the guanine nucleotide binding protein alpha inhibitor 1 (GNAI1), an adenylate cyclase inhibitor which regulates the ATP conversion to cAMP, is a target of miR-124. In physiological conditions, suppression of GNAI1 by miR-124 increases in cAMP activity and leads to an upregulation of *BDNF* expression via cAMP/PKA/CREB pathway. Indeed, alterations in cell metabolism and microRNA environment reflect on the regulation of BDNF.

MiR-124 suppression on BDNF activity negatively influence on neuronal plasticity in various brain regions such as hippocampus and striatum (Bahi, 2016, 2017; Bahi et al., 2014; Bahi & Dreyer, 2013; Chandrasekar & Dreyer, 2009). More recently, (Wei Yang et al., 2020) identified that the miR-124 targets CREB mRNA, consequently downregulating *BDNF* expression, and alters BDNF function via targeting to various gene transcripts downstream TrkB signaling, e.g. PI3K, Akt3 and Ras (Kang et al., 2022). Likewise, miR-124 negatively influence on BDNF signal transduction via suppression of glucocorticoid receptors (S. S. Wang et al., 2017; L. T. Yi et al., 2018), known to enhance TrkB signaling pathways (de Assis & Gasanov, 2019). From another perspective, by testing different exercise intensities, (Mojtahedi et al., 2013) showed that miR-124 levels increase with the intensity, and this increase is amplified in strenuous intensity. BDNF and TrkB also increased but not in strenuous the intensity exercise. The findings indicate a threshold beyond which changes metabolic demands evoke an acute rise in miR-124 levels and suppression.

Amongst the indirect effects seen for microRNA on BDNF, (B. Jiang et al., 2016) study registered that miR-9 upregulates BDNF expression in retinal ganglion cells by suppressing the restrictive silencer factor/RE1-silencing transcription factor (REST), a transcription repressor whose suppression is required for neuronal cell differentiation. Similarly, miR-29c has a positive effect on BDNF expression levels by targeting DNA methyltransferase 3 (G. Yang et al., 2015). The miR-705 was also found in a positive correlation with BDNF levels in ischemic injured brain (Ji et al., 2017). Further, BDNF administration increases miR-214 expression during embryonic stem cells differentiation into endothelial cells (Descamps et al., 2018); and to promote vascular endothelial growth factor-C-dependent lymph angiogenesis by suppressing miR-624-3p in human chondrosarcoma cells (C. Y. Lin et al., 2017).

Final Considerations

Regulation of BDNF by microRNAs involves a dynamic regulation of basic proteins that integrate core mechanisms in neuronal cell homeostasis. This complexity represents a relevant limitation in research towards development of therapeutic strategies. Nevertheless, based on the collection of data, using multiple microRNAs that cooperatively influence on BDNF function might be a prospective strategy for future studies addressing vector-delivery based treatments.

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