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БИОИНФОРМАТИКА

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MiR-485-3p И miR-4728-5p КАК СУПРЕССОРЫ ОПУХОЛЕВОГО РОСТА В ПАТОГЕНЕЗЕ КОЛОРЕКТАЛЬНОГО РАКА[1, 2]

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МикроРНК – класс малых некодирующих РНК, главные функции которых связаны с развитием и прогрессией колоректального рака (CRC), где они действуют как супрессоры опухолевого роста или онкогены. Изучена роль микроРНК miR-485-3p и miR-4728-5p в патогенезе CRC. Образцы опухолей и прилегающих морфологически нормальных тканей получены от 59 больных CRC (37 образцов рака толстой кишки и 22 образца рака прямой кишки). Профили экспрессии miR-485-3p и miR-4728-5p определяли, используя количественную обратную транскрипцию с последующей полимеразной цепной реакцией. Регуляторные сети факторов транскрипции (TF), связанных с микроРНК, конструировали с использованием TransmiR v2.0. Регулируемые TF гены-мишени определяли, используя Human.mirFFL.DB и TRRUST v2.0, функциональную аннотацию и анализ обогащения с помощью DIANA-mirPath v3.0 и -Tarbase v7.0. Показано значительное снижение уровней экспрессии и miR-485-3p, и miR-4728-5p в тканях CRC (кратность изменений составила 0.42 ± 0.70 и 0.59 ± 1.06 соответственно; $p = 0.000$). С другой стороны, более низкие уровни экспрессии miR-485-3p выявлены и в прямой, и в толстой кишке. Более того, снижение уровней экспрессии miR-4728-5p коррелировало с увеличением возраста. Эти различия были статистически незначимыми (FDR-значения p составили 0.126 и 0.168 соответственно). С помощью биоинформатического анализа идентифицированы TF, связанные с miR-485-3p и miR-4728-5p. Некоторые из этих TF, а именно, AR, CREB1, CEBPB, FOXA1, GTF2I, MAZ, NCOR2, NFIC, NRF1, SIN3A, SREBF1, SREBF2, TP53 и YY1, по-видимому, ассоциированные с CRC, выбраны для конструирования потенциальных мишеней сетей микроРНК-TF-ген для ранней диагностики и терапии CRC. Анализ обогащения путей показывает, что сигнальный путь Hippo строго регулируется miR-485-3p. Предполагается, что снижение экспрессии miR-485-3p и miR-4728-5p может быть ассоциировано с развитием CRC.

Ключевые слова: колоректальный рак, микроРНК ОТ-ПЦР, опухолевые супрессоры, факторы транскрипции, биоинформатика

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СПИСОК ЛИТЕРАТУРЫ

1. Global Cancer Observatory (Globocan), International Agency for Research on Cancer. (2020) https://gco.iarc.fr
2. Rabeneck L., Chiu H.M., Senore C. (2020) International perspective on the burden of colorectal cancer and public health effects. *Gastroenterology*. **158**(2), 447–452.
3. Siegel R.L., Miller K.D., Goding Sauer A., Fedewa S.A., Butterly L.F., Anderson J.C., Cercek A., Smith R.A., Jemal A. (2020) Colorectal cancer statistics, (2020). *CA Cancer J. Clin*. **70**, 145–164. https://doi.org/10.3322/caac.21601
4. Sung H., Ferlay J., Siegel R.L., Laversanne M., Soerjomataram I., Jemal A., Bray F. (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin*. **71**(3), 209–249. https://doi.org/10.3322/caac.21660
5. Li J., Guo C., Lu X., Tan W. (2019) Anti-colorectal cancer biotargets and biological mechanisms of puer-

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arin: Study of molecular networks. *Eur. J. Pharmacol.* **858**, 172483. https://doi.org/10.1016/j.ejphar.2019.172483

6. Lv Y., Duanmu J., Fu X., Li T., Jiang Q. (2020) Identifying a new microRNA signature as a prognostic biomarker in colon cancer. *PLoS One*. **15**(2), e0228575. https://doi.org/10.1371/journal.pone.0228575
7. Yang J., Ma D., Fesler A., Zhai H., Leamniramit A., Li W., Wu S., Ju J. (2017) Expression analysis of microRNA as prognostic biomarkers in colorectal cancer. *Oncotarget*. **8**(32), 52403.
8. Balacescu O., Sur D., Cainap C., Visan S., Cruceriu D., Manzat-Saplacan R., Muresan I.S., Balacescu L., Lisencu C., Irimie A. (2018) The impact of miRNA in colorectal cancer progression and its liver metastases. *Int. J. Mol. Sci*. **19**(12), 3711.
9. Tang X.J., Wang W., Hann S. (2019) Interactions among lncRNAs, miRNAs and mRNA in colorectal cancer. *Biochimie*. **163**, 58–72.
10. Wu F., Xing T., Gao X., Liu F. (2019) miR-501-3p promotes colorectal cancer progression via activation of Wnt/β-catenin signaling. *Int. J. Oncol*. **55**(3), 671–683.
11. Motoyama K., Inoue H., Takatsuno Y., Tanaka F., Mimori K., Uetake H., Sugihara K., Mori, M. (2009) Over-and under-expressed microRNAs in human colorectal cancer. *Int. J. Oncol*. **34**(4), 1069–1075.
12. Feng B., Dong T.T., Wang L.L., Zhou H.M., Zhao H.C., Dong F., Zheng M.H. (2012) Colorectal cancer migration and invasion initiated by microRNA-106a. *PLoS One*. **7**(8), e43452.
13. Nishida N., Yamashita S., Mimori K., Sudo T., Tanaka F., Shibata K., Yamamoto H., Ishii H., Doki Y., Mori M. (2012) MicroRNA-10b is a prognostic indicator in colorectal cancer and confers resistance to the chemotherapeutic agent 5-fluorouracil in colorectal cancer cells. *Annals Surgical Oncol.* **19**(9), 3065–3071.
14. Yu Y., Kanwar S.S., Patel B.B., Oh P.S., Nautiyal J., Sarkar F.H., Majumdar A.P. (2012) MicroRNA-21 induces stemness by downregulating transforming growth factor beta receptor 2 (TGFβR2) in colon cancer cells. *Carcinogenesis*. **33**(1), 68–76.
15. Weissmann-Brenner A., Kushnir M., Lithwick Yanai G., Aharonov R., Gibori H., Purim O., Kundel Y., Morgenstern S., Halperin M., Niv Y., Brenner B. (2012) Tumor microRNA-29a expression and the risk of recurrence in stage II colon cancer. *Int. J. Oncol.* **40**(6), 2097–2103.
16. Hwang W.L., Jiang J.K., Yang S.H., Huang T.S., Lan H.Y., Teng H.W., Yang C.Y., Tsai Y.P., Lin C.H., Wang H.W., Yang M.H. (2014) MicroRNA-146a directs the symmetric division of Snail-dominant colorectal cancer stem cells. *Nat. Cell Biol.* **16**(3), 268–280.
17. Zhang W., Zhang T., Jin R., Zhao H., Hu J., Feng, B., Zang L., Zheng M., Wang M. (2014) MicroRNA-301a promotes migration and invasion by targeting TGFBR2 in human colorectal cancer. *J. Exp. Clin. Cancer Res.* **33**(1), 113.
18. Xiao G., Tang H., Wei W., Li J., Ji L., Ge J. (2014) Aberrant expression of microRNA-15a and microRNA-16 synergistically associates with tumor progression and prognosis in patients with colorectal cancer. *Gastroenterol. Res. Prac*. 2014, **364549**. https://doi.org/10.1155/2014/364549
19. Li T., Lai Q., Wang S., Cai J., Xiao Z., Deng D., He L., Jiao H., Ye Y., Liang L., Ding Y., Liao W. (2016) MicroRNA-224 sustains Wnt/β-catenin signaling and promotes aggressive phenotype of colorectal cancer. *J. Exp. Clin. Cancer Res*. **35**, 21. https://doi.org/10.1186/s13046-016-0287-1
20. Zekri A.R.N., Youssef A.S.E.D., Lotfy M.M., Gabr R., Ahmed O.S., Nassar A., Hussein N., Omran D., Medhat E., Eid S., Hussein, M.M., Ismail M.Y., Alenzi F.Q., Bahnassy A.A. (2016) Circulating serum miRNAs as diagnostic markers for colorectal cancer. *PLoS One*. **11**(5), e0154130.
21. Baltruskeviciene E., Schveigert D., Stankevicius V., Mickys U., Zvirblis T., Bublevic J., Suziedelis K., Aleknavicius E. (2017) Down-regulation of miRNA-148a and miRNA-625-3p in colorectal cancer is associated with tumor budding. *BMC Cancer*. **17**(1), 607.
22. Danese E., Minicozzi A.M., Benati M., Paviati E., Lima-Oliveira G., Gusella M., Pasini F., Salvagno G.L., Montagnana M., Lippi G. (2017) Reference miRNAs for colorectal cancer: analysis and verification of current data. *Sci. Rep.* **7**(1), 8413.
23. Yamazaki N., Koga Y., Taniguchi H., Kojima M., Kanemitsu Y., Saito N., Matsumura Y. (2017) High expression of miR-181c as a predictive marker of recurrence in stage II colorectal cancer. *Oncotarget.* **8**(4), 6970.
24. Zhang Y., Guo L., Li Y., Feng G. H., Teng F., Li W., Zhou Q. (2018) MicroRNA-494 promotes cancer progression and targets adenomatous polyposis coli in colorectal cancer. *Mol. Cancer*. **17**(1), 1–11.
25. Ashizawa M., Okayama H., Ishigame T., Min A.K.T., Saito K., Ujiie D., Murakami Y., Kikuchi T., Nakayama Y., Noda M., Tada T., Endo H., Fujita S., Sakamoto W., Saito M., Saze Z., Momma T., Ohki S., Mimura K., Kono K. (2019) miRNA-148a-3p Regulates immunosuppression in DNA mismatch repair–deficient colorectal cancer by targeting PD-L1. *Mol. Cancer Res*. **17**(6), 1403–1413.
26. Du K., Zhang X., Lou Z., Guo P., Zhang F., Wang B., Chen L., Zhang C. (2018) MicroRNA485-3p negatively regulates the transcriptional co-repressor *CtBP1* to control the oncogenic process in osteosarcoma cells. *Int. J. Biol. Sci*. **14**(11), 1445–1456.
27. Yang H, Cho M.E., Li T.W., Peng H., Ko K.S., Mato J.M., Lu S.C. (2013) MicroRNAs regulate the expression of methionine adenosyltransferase 1A in hepatocellular carcinoma. *J. Clin. Res*. **123**(1), 285–298.
28. Wang Z.Q., Zhang M.Y., Deng M.L., Weng N.Q., Wang H.Y., Wu S.X. (2017) Low serum level of miR-485-3p predicts poor survival in patients with glioblastoma. *PLoS One*. **12**(9), e0184969.
29. Formosa A., Markert E.K., Lena A.M., Italiano D., Finazzi-Agro E., Levine A.J., Bernardini S., Garabadgiu A.V., Melino G., Candi E. (2014) MicroRNAs, miR-154, miR-299-5p, miR-376a, miR-376c, miR-377, miR-381, miR-487b, miR-485-3p, miR-495 and miR-654-3p, mapped to the 14q32. 31 locus, regulate proliferation, apoptosis, migration and invasion in metastatic prostate cancer cells. *Oncogene*. **33**(44), 5173–5182.

30. Wang J., Zhang H., Zhou X., Wang T., Zhang J.Y., Zhu W., Zhu H., Cheng W. (2018) Five serum-based miRNAs were identified as potential diagnostic biomarkers in gastric cardia adenocarcinoma. *Cancer Biomark*. **23**(2), 193–203.

31. Lou C., Xiao M., Cheng S., Lu X., Jia S., Ren Y., Li Z. (2016) MiR-485-3p and miR-485-5p suppress breast cancer cell metastasis by inhibiting PGC-1 α expression. *Cell Deat Dis.* **7**(3), e2159.

32. Mizuno K., Mataki H., Arai T., Okato A., Kamikawaji K., Kumamoto T., Hiraki T., Hatanaka K., Inoue H., Seki N. (2017) The microRNA expression signature of small cell lung cancer: tumor suppressors of miR-27a-5p and miR-34b-3p and their targeted oncogenes. *J. Hum. Genet*. **62**(7), 671–678.

33. Zhao Z., Gao D., Ma T., Zhang L. (2019) MicroRNA-141 suppresses growth and metastatic potential of head and neck squamous cell carcinoma. *Aging*. **11**(3), 921–932.

34. Li H., Zhou X., Zhu J., Cheng W., Zhu W., Shu Y., Liu P. (2015) MiR-4728-3p could act as a marker of HER2 status. *Cancer Biomarkers*. **15**(6), 807–814.

35. Schmitt D.C., Madeira da Silva L., Zhang W., Liu Z., Arora R., Lim S., Schuler A.M., McClellan S., Andrews J.F., Kahn A.G., Zhou M., Ahn E.Y., Tan M. (2015) ErbB2-intronic microRNA-4728: a novel tumor suppressor and antagonist of oncogenic MAPK signaling. *Cell Death Dis*. **6**(5), e1742.

36. Jiashi W., Chuang Q., Zhenjun Z., Guangbin W., Bin L., Ming H. (2018) MicroRNA-506-3p inhibits osteosarcoma cell proliferation and metastasis by suppressing RAB3D expression. *Aging*. **10**(6), 1924–1305.

37. Livak K.J., Schmittgen T.D. (2001) Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta CT}$ method. *Methods*. **25**(4), 402–408. https://doi.org/10.1006/meth.(2001)1262

38. Benjamini Y., Hochberg Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Statist. Soc. B. Methodol*. **57**(1), 289–300.

39. TransmiR v2.0 database. http://www.cuilab.cn/transmir

40. Tong Z., Cui Q., Wang J., Zhou Y. (2019) TransmiR v2.0: an updated transcription factor-microRNA regulation database. *Nucleic Acids Res*. **8**(47), D253–D258.

41. Human.mirFFL.DB. http://www.mirffldb.in/human/

42. TRRUST v2.0 (Transcriptional Regulatory Relationships Unraveled by Sentence-based Text-mining). https://www.grnpedia.org/trrust/

43. The human protein atlas. https://www.proteinatlas.org

44. DIANA-mirPath v3.0. http://www.microrna.gr/miRPathv2

45. DIANA-TarBase v7.0. http://www.microrna.gr/tarbase

46. Vlachos I.S., Zagganas K., Paraskevopoulou M.D., Georgakilas G., Karagkouni D., Vergoulis T., Dalamagas T., Hatzigeorgiou A.G. (2015) DIANA-miRPath v3.0: deciphering microRNA function with experimental support. *Nucleic Acids Res*. **43**(W1), W460–W466.

47. KEGG pathway database. https://www.genome.jp/kegg/pathway.html

48. Hao S., Huo S., Du Z., Yang Q., Ren M., Liu S., Liu T., Zhang G. (2019) MicroRNA-related transcription factor regulatory networks in human colorectal cancer. *Medicine*. **98**(15), e15158. https://doi.org/10.1097/MD.0000000000015158

49. Huang H.Y., Lin Y.C.D., Li J., Huang K.Y., Shrestha S., Hong H.C., Tang Y., Chen Y.G., Jin C.N., Yu Y., Xu J.T., Li Y.M., Cai X.X., Zhou Z.Y., Chen X.H., Pei Y.Y., Hu L., Su J.J., Cui S.D., Wang F., Xie Y.Y., Ding S.Y., Luo M.F., Chou C.H., Chang N.W., Chen K.W., Cheng Y.H., Wan X.H., Hsu W.L., Lee T.Y., Wei F.X., Huang H.D. (2020) miRTarBase 2020: updates to the experimentally validated microRNA–target interaction database. *Nucleic Acids Res.* **48**(D1), D148–D154.

50. Wang H., Wang N., Zheng X., Wu L., Fan C., Li X., Fan C., Li X., Ye K., Han S. (2021) Circular RNA hsa_circ_0009172 suppresses gastric cancer by regulation of microRNA-485-3p-mediated NTRK3. *Cancer Gene Ther*. **28**(12), 1312–1324.

51. Chiang Y., Song Y., Wang Z., Liu Z., Gao P., Liang J., Zhu J., Xing C., Xu H. (2012) microRNA-192-194 and-215 are frequently downregulated in colorectal cancer. *Exp. Ther. Med*. **3**(3), 560–566.

52. Zhang Y., Sui R., Chen Y., Liang H., Shi J., Piao H. (2019) Downregulation of miR-485-3p promotes glioblastoma cell proliferation and migration via targeting RNF135. *Exp. Ther. Med*. **18**(1), 475–482.

53. Han D.L., Wang L.L., Zhang G.F., Yang W.F., Chai J., Lin H.M., Fu Z., Yu J.M. (2019) MiRNA-485-5p, inhibits esophageal cancer cells proliferation and invasion by down-regulating O-linked N-acetylglucosamine transferase. *Eur. Rev. Med. Pharmacol. Sci*. **23**(7), 2809–2816.

54. Chen Z., Li Q., Wang S., Zhang J. (2015) miR-485-5p inhibits bladder cancer metastasis by targeting HMGA2. *Int. J. Mol. Med*. **36**(4), 1136–1142.

55. Taherdangkoo K., Nezhad, S.K., Hajjari M.R., Birgani M.T. (2020) MiR-485-3p suppresses colorectal cancer via targeting TPX2. *Bratisl. Lek. Listy*. **121**(4), 302–307.

56. Chen C.F., He X., Arslan A.D., Mo Y.Y., Reinhold W.C., Pommier Y., Beck W.T. (2011) Novel regulation of nuclear factor-YB by *miR-485-3p* affects the expression of DNA topoisomerase IIα and drug responsiveness. *Mol. Pharmacol*. **79**(4), 735–741.

57. Yao X., Cui X., Wu X., Xu P., Zhu W., Chen X., Zhao T. (2018) Tumor suppressive role of miR-1224-5p in keloid proliferation, apoptosis and invasion via the TGF-b1/Smad3 signaling pathway. *Biochem. Biophys. Res. Commun*. **495**, 713–720.

58. Zhou Y., Yuan Y., Li L., Wang X., Quan Y., Liu C., Yu M., Hu X., Meng X., Zhou Z., Zhang C.Y., Chen X., Liu M., Wang C. (2021) HER2-intronic miR-4728-5p facilitates HER2 expression and accelerates cell proliferation and migration by targeting EBP1 in breast cancer. *PloS One*. **16**(2), e0245832.

59. Ghodssi-Ghassemabadi R., Hajizadeh E., Kamian S., Mahmoudi M. (2019) Clinicopathological features and survival of colorectal cancer patients younger than 50 years: a retrospective comparative study. *J. Egypt. Natl. Cancer Inst*. **31**(1), 6. https://doi.org/10.1186/s43046-019-0006-z

60. Sun M., Song H., Wang S., Zhang C., Zheng L., Chen F., Shi D., Chen Y., Yang C., Xiang Z., Liu Q., Wei C., Xiong B. (2017) Integrated analysis identifies microRNA-195 as a suppressor of Hippo-YAP pathway in colorectal cancer. *J. Hematol. Oncol.* **10**(1), 79. https://doi.org/10.1186/s13045-017-0445-8
61. Qu R., Hao S., Jin X., Shi G., Yu Q., Tong X., Guo D. (2018) MicroRNA-374b reduces the proliferation and invasion of colon cancer cells by regulation of LRH-1/Wnt signaling. *Gene*. **642**, 354–361.
62. Zhang J., Zhang K., Bi M., Jiao X., Zhang D., Dong Q. (2014) Circulating microRNA expressions in colorectal cancer as predictors of response to chemotherapy. *Anti-Cancer Drugs*. **25**(3), 346–352.
63. Poel D., Gootjes E.C., Bakkerus L., Trypsteen W., Dekker H., van der Vliet H.J., van Grieken N.C.T, Verhoef C., Buffart T.E., Verheul H.M. (2020) A specific microRNA profile as predictive biomarker for systemic treatment in patients with metastatic colorectal cancer. *Cancer Med.* **9**(20), 7558–7571.
64. Wang Y., Xu X., Maglic D., Dill M.T., Mojumdar K., Ng P.K.S., Jeong K.J., Tsang Y.H., Moreno D., Bhavana V.H., Peng X., Ge Z., Chen H., Li J., Chen Z., Zhang H., Han L., Du D., Creighton C.J., Mills G.B., Cancer Genome Atlas Research Network, Camargo F., Liang H. (2018) Comprehensive molecular characterization of the Hippo signaling pathway in cancer. *Cell Rep.* **25**(5), 1304–1317.
65. Triner D., Castillo C., Hakim J.B., Xue X., Greenson J.K., Nuñez G., Chen G.Y., Colacino J.A., Shah Y.M. (2018) Myc-associated zinc finger protein regulates the proinflammatory response in colitis and colon cancer via STAT3 signaling. *Am. Soc. Microbiol. Mol. Cell. Biol.* **38**(22), e00386–18. https://doi.org/10.1128/MCB.00386-18
66. Ye Q., Su L., Chen D., Zheng W., Liu Y. (2017) Astragaloside IV induced miR-134 expression reduces EMT and increases chemotherapeutic sensitivity by suppressing CREB1 signaling in colorectal cancer cell line SW-480. *Cell Physiol. Biochem.* **43**, 1617–1626.
67. Ramos A., Camargo F.D. (2012) The Hippo signaling pathway and stem cell biology. *Trends Cell Biol.* **22**(7), 339–346.
68. Zhou G.X., Li X.Y., Zhang Q., Zhao K., Zhang C.P., Xue C.H., Yang K., Tian Z.B. (2013) Effects of the Hippo signaling pathway in human gastric cancer. *Asian Pacific J. Cancer Prev.* **14**(9), 5199–5205.
69. Hong A.W., Meng Z., Guan K.L. (2016) The Hippo pathway in intestinal regeneration and disease. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 324–337.
70. Liu Y., Wang G., Yang Y., Mei Z., Liang Z., Cui A., Wu T., Liu C.Y., Cui L. (2016) Increased TEAD4 expression and nuclear localization in colorectal cancer promote epithelial-mesenchymal transition and metastasis in a YAP-independent manner. *Oncogene*. **35**, 2789–2800.
71. Richter J., Ullah K., Xu P., Alscher V., Blatz A., Peifer C., Halekotte J., Leban J., Vitt D., Holzmann K., Bakulev V., Pinna L.A., Henne-Bruns D., Hillenbrand A., Kornmann M., Leithauser F., Bischof J., Knippschild U. (2015) Effects of altered expression and activity levels of CK1d and E on tumor growth and survival of colorectal cancer patients. *Int. J. Cancer.* **136**, 2799–2810.
72. Hardy K.M., Booth B.W., Hendrix M.J., Salomon D.S., Strizzi L. (2010) ErbB/EGF signaling and EMT in mammary development and breast cancer. *J. Mammary Gland Biol. Neoplasia*. **15**(2), 191–199.
73. Catto J.W., Alcaraz A., Bjartell A.S., White R.D.V., Evans C.P., Fussel S., Hamdy F.C., Kallioniemi O., Mengual L., Schlomm T., Visakorpi T. (2011) MicroRNA in prostate, bladder, and kidney cancer: a systematic review. *Eur. Urol.* **59**(5), 671–681.
74. Harb J., Lin P.J., Hao J. (2019) Recent development of Wnt signaling pathway inhibitors for cancer therapeutics. *Curr. Oncol. Rep.* **21**(2), 12.
75. Rahmani F., Ferns G.A., Talebian S., Nourbakhsh M., Avan A., Shahidsales S. (2020) Role of regulatory miRNAs of the PI3K/AKT signaling pathway in the pathogenesis of breast cancer. *Gene*. **737**, 144459.

miR-485-3p AND miR-4728-5p AS TUMOR SUPPRESSORS IN PATHOGENESIS OF COLORECTAL CANCER

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MicroRNAs (miRNAs) are a class of small noncoding RNAs that have major functions in the development and progression of colorectal cancer (CRC) as tumor suppressors or oncogenes. The aim of the current research was to assess the role of miR-485-3p and miR-4728-5p in the pathogenesis of CRC. In this study, fresh tumor and adjacent non-tumor tissue samples were obtained from a total of 59 CRC patients, 37 from colon and 22 from rectum. The expression profiles of miR-485-3p and miR-4728-5p were determined using qRT-PCR. miRNA-related transcription factor (TF) regulatory networks were constructed using the TransmiR v2.0, TF-regulated target genes were determined using the Human.mirFFL.DB and TRRUST v2.0, functional annotation and pathway enrichment analyses were performed using DIANA-mirPath v3.0 and -Tarbase v7.0. The results demonstrated that the expression levels of both miR-485-3p and miR-4728-5p were

very significantly downregulated in CRC tissues (fold changes = 0.42 ± 0.70 and 0.59 ± 1.06, respectively; both $p = 0.000$). On the other hand, lower expression levels of miR-485-3p were detected in the both rectum and colon. Moreover, the decrease in the expression levels of miR-4728-5p was correlated with increasing age. However, these differences were not statistically significant according to the FDR-related p-values (0.126 and 0.168, respectively). By bioinformatics analyses, miR-485-3p and miR-4728-5p-related TFs were identified. Some of these TFs, namely, AR, CREB1, CEBPB, FOXA1, GTF2I, MAZ, NCOR2, NFIC, NRF1, SIN3A, SREBF1, SREBF2, p53 and YY1, appeared to be associated with CRC and were, therefore, selected to construct miRNA–TF-gene networks of potential targets for the early diagnosis and treatment of CRC. Pathway enrichment analysis indicated Hippo signaling pathway as heavily regulated by miR-485-3p. It seems that the decrease in expression levels of miR-485-3p and miR-4728-5p might be associated with development of colorectal cancer.

Keywords: colorectal cancer, qRT-PCR, microRNA, tumor suppressor, transcription factor, bioinformatics