

# MicroRNA Signature Targeting Transient Receptor Potential Channels in the Prognosis and Therapy of Cancer

Giorgio Santoni<sup>1\*</sup>, Consuelo Amantini<sup>2</sup>, Massimo Nabissi<sup>1</sup>, Federica Maggi<sup>1,3</sup>, Maria Beatrice Morelli<sup>1</sup>

<sup>1</sup>School of Pharmacy, Section of Immunopathology, University of Camerino, Camerino, Italy

<sup>2</sup>School of Bioscience and Veterinary Medicine, University of Camerino, Camerino, Italy

<sup>3</sup>Department of Molecular Medicine, University of Rome Sapienza, Rome, Italy

\*Correspondence should be addressed to Giorgio Santoni; [giorgio.santoni@unicam.it](mailto:giorgio.santoni@unicam.it)

**Received date:** February 12, 2020, **Accepted date:** March 19, 2020

**Copyright:** © 2020 Santoni G, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that modulate protein-coding mRNAs. Numerous miRNAs are expressed in human and 50% of human miRNAs are associated with carcinogenesis. Specific miRNAs are expressed in different cancer tissues and modulation of their expression is associated to different tumor stages and clinical outcomes. miRNAs control the transcription of different genes involved in the neoplastic transformation and tumor progression by regulating oncogenes and tumor-suppressor genes. Among genes regulated by miRNAs, an emerging role of miRNA signature for the transient receptor potential (TRP) ion channels in cancer prognosis and therapy has been reported. By gaining the functional role of miRNA signature in different cancers, a specific miRNA-target genes for Wnt/ $\beta$ -catenin, TRP channel and inflammatory signaling pathways has been found to contribute to tumorigenesis. Moreover, the identification of miRNA signature may have prognostic value and correlate with overall survival in different cancer patients. Modulation of miRNA levels can induce or overcome chemotherapy resistance and genetic and epigenetic mechanisms and alteration of RNA genesis result in altered therapy response. Overall, further studies are required to completely understand the potential application in prognosis and therapy of miRNA-targeting TRP mRNA.

**Keywords:** microRNA, TRP, Biomarkers, Cancer

## Introduction

This short communication would be the continuation of the Santoni's paper entitled "Targeting Transient Receptor Potential Channels by MicroRNAs drives tumor development and progression" published in: Calcium Signaling, Advances in Experimental Medicine and Biology [1].

MicroRNAs (miRNAs) are small non-coding RNAs that negatively modulate post-transcriptional protein-coding mRNAs. It is estimated that numerous miRNAs are expressed in human and more than 700 miRNAs have been documented to date [2]. About 50% of human miRNAs are found in regions of sites called "brittle", which are associated with carcinogenesis [3]. The evidence

available so far has shown that miRNAs participate extensively in the development or progression of many types of tumors of various origins; clinical tests can be used to classify this pathology based on the molecular profiles of miRNAs.

Specific miRNAs are expressed in different cancer tissues and modulation of their expression are associated to tumorigenesis [3]. Herein we are going to focus our attention on their employment in clinical oncology as prognostic biomarkers as well as their use in cancer therapy. The use of sets of miRNAs, and not a single miRNA, allows building a cancer specific miRNA signature. In fact, recently it has been reported that the characterization of specific miRNA signature in different cancer types not only plays an important role in cancer

transformation and progression as well as in early diagnosis, but it answers also for the possibility to employ miRNAs as novel prognostic markers in cancer. On this basis, a specific target gene network and the cellular processes regulated by and the intracellular signaling pathways could be parallelly identified. Moreover, the identification of miRNA differentially expressed in the early or late-stage (DEmiRNAs), permits [4] to build a risk score and on this basis, to stratify the cancer patients in high-risk and low-risk populations showing different overall survival (OS) [5].

MiRNAs were initially discovered as a small temporal RNA (strRNA) in *C. elegans* in 1993 [6]; however, initially this discovery did not arouse much interest, until seven years later when Let-7 (the second miRNA) was identified [7]. In subsequent years, researchers have shown that miRNAs are part of a large family of small non-coding RNAs that exist in species ranging from plants to humans [8-10]. MiRNAs are small strands of endogenous non-coding RNA formed by approximately 22 bp aimed at the 3' untranslated region (UTR) of mRNA. The miRNAs encoded by the human genome are different and a single miRNA can modulate different genes. From this, several studies have shown that miRNA functions are not limited to temporal regulation, but are implicated in various biological processes such as cell cycle and proliferation, apoptosis and development [11,12]. MiRNAs are able to control the transcription of different genes involved in the neoplastic transformation and tumor progression through the regulation of the expression of both oncogenes and tumor-suppressor genes [13,14]. In 2002, the first direct evidence of the role of miRNA in human cancer was presented; Calin and colleagues found that miR-15 and miR-16 play a crucial role in chronic lymphatic leukaemia [15]. Subsequently, other examples of mRNAs targeted to TRP ion channels related to human tumors were identified [16].

Among the genes involved in the transformation and progression of cancer, an important role is played by ion channels and in particular by the transient receptor potential (TRP) channels which expression and functions are regulated also at miRNA level [1].

Esophageal squamous cell carcinoma (ESCC) represents the major esophageal cancer type, with about 400,000 cases in the world, a poor prognosis, with an OS less of 20% at five-years. Yu et al. [17] have reported the characterization of a five-miRNA signature as prognostic biomarkers in ESCCs. A total of 46 DEmiRNAs have been identified in early and late ESSC tumor stages. On the basis of statistical analysis, five prognostic miRNAs (miR-181c-5p, miR-195-5p, miR-203, miR-212-3p and miR-28-5p)

and relative risk score, characterizing two different high-risk and low-risk mortality in ESSC patients have been reported [17]. The analysis of the expression of these miRNAs found in the ESCC miRNA signature evidenced that their expression is also altered in other cancer types. Thus, MiR-181c-5p is up-regulated in pancreatic cancer compared to chronic pancreatitis controls [18], whereas miR-195-5p is up-regulated in laryngeal squamous cell carcinoma patients compared to healthy subjects [19]; miR-203 represents a prognostic marker in pancreatic cancer [20] and down-regulation of miR-212-3p results in radio-resistance in nasopharyngeal carcinoma [21]. Finally, in renal cell carcinoma serum miR-28-5p is down-regulated and plays a tumor suppressive role [22].

By gaining the functional role of the five miRNA signature in ESCCs, Yu et al., also unveiled a specific miRNA-target genes and signaling profile patterns, evidencing as the altered Wnt/ $\beta$ -catenin [23], cGMP-PKG [24], TRP channel [25,26], estrogen signaling pathways [27] and the inflammation status [28] contribute to tumorigenesis and show prognostic value in ESSC patients. However, a larger cohort of ESSC patients of that used by Yu et al (119 patients) are needed to completely validate the prognostic mean of miRNA signature in ESCCs.

TRPM4 overexpression and miR-150 down-regulation as well as Wnt/ $\beta$ -catenin pathway and epithelial mesenchymal transition (EMT) stimulation are evidenced in prostate cancer (PCa) tissues [29]. TRPM4 is a direct target of miR-150 and miR-150 overexpression abrogates the  $\beta$ -catenin signaling pathway. TRPM4 knockdown or miR-150 increased expression, suppress EMT, proliferation, migration/invasion *in vitro* and reduced tumor growth and metastatic spreading *in vivo*, thus inhibiting the progression of PCa [29].

TRPM6 is involved in the physiology of  $Mg^{2+}$ . TRPM6 mutations are associated with hypomagnesemia [30]. Many studies have documented that hypomagnesemia could promote tumor metastasis. High hsa-let-7g expression levels, as well as hsa-let-7f-1 are closely associated with development of colorectal cancer (CRC) [31]. A role in the survival and prognosis of hsa-let-7g and hsa-let-7f-1 miRNAs targeting TRPM6 has been found in CRC. A marked down-regulation of TRPM6 and hsa-let-7g and hsa-let-7f-1 upregulation was evidenced in about 80% of CRC tissues, compared with their paired normal colon mucosal tissues. TRPM6 is one of the top 10 genes (SPARC, CXCL3, COL9A3, FABP1, CLDN2 up-regulated and CA4, CHGA, AKR1B10, FXYP3 and TRPM6 down-regulated) screened in CRC. On the contrary high TRPM6 expression in CRC is indicative of a prolonged OS [32].

TRPM7 plays an oncogenic role in several human

cancer and suggested to be a molecular target for several miRNAs in cancer diseases. The miR-543/TRPM7 axis is involved in cervical cancer (CC) and the levels of miR-543 represent a potential biomarker for CC diagnosis, prognosis and therapy [33]. Mir-543 has been found to localize in the DLK1-DIO3 region of human chromosome 14 [34]. By dual luciferase assay it has been demonstrated that miR-543 directly binds to the 3'-UTR of TRPM7, and modulates its expression. Altered miR-543 expression has been evidenced in different cancer types. In CC, miR-543 is down-regulated, and this reduced expression is accompanied by up-regulation of the TRPM7 channel. Reduced expression of miR-543 correlates with poor prognosis as a consequence of increased tumor size, high pathological stage and lymph-nodes metastasis. In fact, miR-543 down-regulation induces cell cycle progression and proliferation of aggressive CC cells, promotes the migration and invasion, inhibits the apoptotic cell death *in vitro* and stimulates tumor growth *in vivo* in a xenograft model [33]. The phosphoinositide 3 kinase/protein kinase B (PI3K/AKT) and p38/mitogen-activated protein kinase (p38/MAPK) signaling pathways promote the miR-543/TRPM7-mediated progression of CC cells. Activation of PI3K/AKT and p38/MAPK signaling pathways is inhibited by miR-543 overexpression, but recovered by restoration of TRPM7 expression. Thus, miR-543 in CCs may represent a novel therapeutic biomarker. In a same way, miR-129-3p directly targets TRPM7 and acts as negative regulator of TRPM7 expression in clear cell renal cell carcinoma (ccRCC) [35], the most frequent kidney cancer in China, with about 50% to 70% disease-specific survival at 5-years [36]. However, because of lack of early diagnosis and resistance to radio- and chemo-therapy, the survival of metastatic ccRCC patients is about one year [37] and the identification of prognostic biomarkers is very important.

MiRNA-150 has been found to suppress EMT, invasion and metastasis in PCa through the TRPM4-mediated  $\beta$ -catenin signaling pathway [29].

Overexpression, silencing or switching off specific miRNAs has been described in glioblastoma (GBM) [38,39]. Several studies have reported that miRNA signature may also be a prognostic indicator of GBM [40]. A recent report evidences the capability of miRNA signature to discriminate different glioma stem cells (GSCs) clusters characterized by different clinical feature in GBM. A specific microRNA signature consisting of three microRNAs: miR-23a, miR-27a and miR-9-3p has been found to discriminate the pro-neural- and mesenchymal-like phenotypes in GSC and primary GBMs [41]. Reduced miR-9-3p and enhanced miR-23a and miR27a expression marks preferentially the GBMs with

mesenchymal signature, which is associated with a more aggressive and invasive behavior. Interestingly, by down regulation of JAK/STAT pathway, miR-9-3p drives the GSC differentiation *vs* mesenchymal type. Moreover, the typical EGFvIII variant expression in GBM with tumor growth advantage, frequently show a mesenchymal phenotype [42]. Thus, new knowledge of miRNA in cancer highlights new way to stratify different stages of neoplastic disease and tailor an appropriate therapy to specific GBM patient subsets.

Many deregulated miRNAs have been found in cancers. Because the tissue specificity of miRNA regulation, one miRNA can target different mRNAs and one mRNA can be targeted by different miRNAs and also opposite effects can be induced in different cancer cell types. Some miRNA can promote drug resistance, instead to enhance the therapeutic effect. A lot of examples could be provided in this way and modulation of miRNA levels can induce or overcome chemotherapy resistance. In this regard, gain or loss of miRNA genes, epigenetic regulation, deregulation of transcription factors, alteration of the mechanisms regulating RNA genesis can result in altered therapy response. A methylation-based regulatory network for miRNA-320a is evidenced in chemo-resistant breast cancer (BC) [43]. It has been previously demonstrated that overexpression of TRPC5 and nuclear factor of activated T-cells isoform c3 (NFATC3) are essential for cancer chemoresistance [4], however the epigenetic mechanism undergoing this effect has been only recently demonstrated [43]. MiRNA-320a that directly targets TRPC5 and NFATC3 was found to be down-regulated in chemo resistant cancer cells. Hypomethylation of the promoter of miRNA-320a as well as of the v-ets erythroblastosis virus E26 oncogene homolog 1, which inhibited miRNA-320a expression represents a significant unfavorable predictor for clinical outcome in BC patients [43].

## Conclusion

The knowledge on miRNA have open a new way in understanding human cancer. Herein we have focused our attention mainly on the prognostic and therapeutic role of miRNA in cancer disease. Dis-regulated expression of miRNA in cancer is associated with worse prognosis also in consequence of the induction of chemotherapy drug-resistance in different cancer types. Since the heterogeneity of cancer and the pleiotropic effects of miRNA, only miRNAs well studied *in vitro* and *in vivo* could be used for clinical application. Moreover, although the miRNAs show high efficiency and safety, more important is their targeting into tumor cells.

MiRNA could be used alone or in combination with

chemotherapy. Thus, miRNA-27b synergizes with a variety of anti-cancer agents by activation of the p53 tumor suppressor gene and CYP1B1 suppression [44]. Improved efficiency in delivery of miRNA drugs are arrived by nanotechnology. In PDAC, the encapsulation in nano-carrier of miRNA-205 with GEM or miRNA-34a with doxorubicin (DOX) in BC have increased the therapeutic effects and reduced the side adverse effects. In this regard, a role for miRNA-34a/p53 axis in TRPV1-mediated drug-resistant cancer cells may be suggested [45].

Modulation of miRNA levels can induce or overcome chemotherapy resistance. In this regard, gain or loss of miRNA genes, epigenetic regulation, deregulation of transcriptional factors, alteration of the mechanisms regulating RNA genesis can result in altered therapy response.

Thus, miRNA-21 promotes DOX resistance in BC. On the contrary, miRNA-137, miRNA-149 or miRNA-181a all could reduce DOX resistance in BC cells. The process of miRNA biogenesis and processing could also be dysregulated in cancer cells. Transfection of MCF7/DOX-resistant cells with miRNA-541 that target the MDR1 gene induces increased sensitivity of cancer cells to DOX, suggesting that changes in miRNA levels may have implication in the reversion of cancer-resistance in these cells [46]. A role of TRPV2 and TRPM2 in the sensitization of cancer cells (e.g., glioblastoma and gastric cancer cells) to DOX has been provided [47,48].

Sorafenib resistance is common in HCC patients. MiRNA-193b down-regulation is reported in HBV-positive HCCs. Restoring miRNA-193b levels re-sensitizes HCC cells to sorafenib-induced apoptosis [49]. A role for TRPV1 in the pathogenesis of HCC and on the effects of sorafenib alone or in synergism with capsaicin, the synthetic ligand of TRPV1 channel has been suggested [50].

Overall, the studies on the involvement of miRNA targeting different channels belonging to the TRP family in cancer cells must to be improved to completely understand the potential application in prognosis and cancer therapy.

## Funding

MBM was supported by the Fondazione Umberto Veronesi (Post-doctoral Fellowship 2019).

## Author Contributions

GS writing—original draft preparation; CA, MN, FM, MBM review and editing.

## References

1. Santoni G, Morelli MB, Santoni M, Nabissi M, Marinelli O, Amantini C. Targeting Transient Receptor Potential Channels by MicroRNAs Drives Tumor Development and Progression. In *Calcium Signaling 2020* (pp. 605-623). Springer, Cham.
2. Großhans H, Filipowicz W. The expanding world of small RNAs. *Nature*. 2008 Jan;451(7177):414-6.
3. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR. MicroRNA expression profiles classify human cancers. *Nature*. 2005 Jun;435(7043):834-8.
4. Ma X, Chen Z, Hua D, He D, Wang L, Zhang P, Wang J, Cai Y, Gao C, Zhang X, Zhang F. Essential role for TrpC5-containing extracellular vesicles in breast cancer with chemotherapeutic resistance. *Proceedings of the National Academy of Sciences*. 2014 Apr 29;111(17):6389-94.
5. Feng A, Yuan X, Li X. MicroRNA-345 inhibits metastasis and epithelial-mesenchymal transition of gastric cancer by targeting FOXQ1. *Oncology Reports*. 2017 Nov 1;38(5):2752-60.
6. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993 Dec 3;75(5):843-54.
7. Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G. The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. *Nature*. 2000 Feb;403(6772):901-6.
8. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science*. 2001 Oct 26;294(5543):853-8.
9. Ambros V. The functions of animal microRNAs. *Nature*. 2004 Sep;431(7006):350-5.
10. Ambros V. MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. *Cell*. 2003 Jun 13;113(6):673-6.
11. Croce CM, Calin GA. miRNAs, cancer, and stem cell division. *Cell*. 2005 Jul 15;122(1):6-7.
12. Tong AW, Nemunaitis J. Modulation of miRNA activity in human cancer: a new paradigm for cancer gene therapy?. *Cancer Gene Therapy*. 2008 Jun;15(6):341-55.

13. Harada K, Baba Y, Ishimoto T, Shigaki H, Kosumi K, Yoshida N, Watanabe M, Baba H. The role of microRNA in esophageal squamous cell carcinoma. *Journal of Gastroenterology*. 2016 Jun 1;51(6):520-30.
14. Chang JC, Kundranda M. Novel diagnostic and predictive biomarkers in pancreatic adenocarcinoma. *International Journal of Molecular Sciences*. 2017 Mar;18(3):667.
15. Calin GA, Cimmino A, Fabbri M, Ferracin M, Wojcik SE, Shimizu M, Taccioli C, Zanesi N, Garzon R, Aqeilan RI, Alder H. MiR-15a and miR-16-1 cluster functions in human leukemia. *Proceedings of the National Academy of Sciences*. 2008 Apr 1;105(13):5166-71.
16. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Alder H, Rattan S, Keating M, Rai K, Rassenti L. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proceedings of the National Academy of Sciences*. 2002 Nov 26;99(24):15524-9.
17. Yu J, Zhu M, Lv M, Wu X, Zhang X, Zhang Y, Li J, Zhang Q. Characterization of a five-microRNA signature as a prognostic biomarker for esophageal squamous cell carcinoma. *Scientific Reports*. 2019 Dec 27;9(1):1-1.
18. Kaur S, Krishn SR, Rachagani S, Batra SK. Significance of microRNA-based biomarkers for pancreatic cancer. *Annals of Translational Medicine*. 2015 Oct;3(18).
19. Ayaz L, Görür A, Yaroğlu HY, Özcan C, Tamer L. Differential expression of microRNAs in plasma of patients with laryngeal squamous cell carcinoma: potential early-detection markers for laryngeal squamous cell carcinoma. *Journal of Cancer Research and Clinical Oncology*. 2013 Sep 1;139(9):1499-506.
20. Greither T, Grochola LF, Udelnow A, Lautenschläger C, Würfl P, Taubert H. Elevated expression of microRNAs 155, 203, 210 and 222 in pancreatic tumors is associated with poorer survival. *International Journal of Cancer*. 2010 Jan 1;126(1):73-80.
21. PLOS ONE Staff. Correction: Genome-Wide Analyses of Radioresistance-Associated miRNA Expression Profile in Nasopharyngeal Carcinoma Using Next Generation Deep Sequencing. *PloS one*. 2014 Oct 1;9(10):e110099.
22. Wang C, Wu C, Yang Q, Ding M, Zhong J, Zhang CY, Ge J, Wang J, Zhang C. miR-28-5p acts as a tumor suppressor in renal cell carcinoma for multiple antitumor effects by targeting RAP1B. *Oncotarget*. 2016 Nov 8;7(45):73888.
23. Salahshor S, Naidoo R, Serra S, Shih W, Tsao MS, Chetty R, Woodgett JR. Frequent accumulation of nuclear E-cadherin and alterations in the Wnt signaling pathway in esophageal squamous cell carcinomas. *Modern Pathology*. 2008 Mar;21(3):271-81.
24. Shi P, Sun J, He B, Song H, Li Z, Kong W, Wang J, Wang J, Xue H. Profiles of differentially expressed circRNAs in esophageal and breast cancer. *Cancer Management and Research*. 2018;10:2207.
25. Ding X, He Z, Shi Y, Wang Q, Wang Y. Targeting TRPC6 channels in oesophageal carcinoma growth. *Expert Opinion on Therapeutic Targets*. 2010 May 1;14(5):513-27.
26. Chen Z, Li J, Tian L, Zhou C, Gao Y, Zhou F, Shi S, Feng X, Sun N, Yao R, Shao K. MiRNA expression profile reveals a prognostic signature for esophageal squamous cell carcinoma. *Cancer Letters*. 2014 Aug 1;350(1-2):34-42.
27. Zhang Z, He Q, Fu S, Zheng Z. Estrogen Receptors in Regulating Cell Proliferation of Esophageal Squamous Cell Carcinoma: Involvement of Intracellular Ca<sup>2+</sup> Signaling. *Pathology & Oncology Research*. 2017 Apr 1;23(2):329-34.
28. Liu JS, Huang Y, Yang X, Feng JF. A nomogram to predict prognostic values of various inflammatory biomarkers in patients with esophageal squamous cell carcinoma. *American Journal of Cancer Research*. 2015;5(7):2180.
29. Hong X, Yu JJ. MicroRNA-150 suppresses epithelial-mesenchymal transition, invasion, and metastasis in prostate cancer through the TRPM4-mediated  $\beta$ -catenin signaling pathway. *American Journal of Physiology-Cell Physiology*. 2019 Apr 1;316(4):C463-80.
30. Lainez S, Schlingmann KP, Van Der Wijst J, Dworniczak B, Van Zeeland F, Konrad M, Bindels RJ, Hoenderop JG. New TRPM6 missense mutations linked to hypomagnesemia with secondary hypocalcemia. *European Journal of Human Genetics*. 2014 Apr;22(4):497-504.
31. Wang J, Mouradov D, Wang X, Jorissen RN, Chambers MC, Zimmerman LJ, Vasaikar S, Love CG, Li S, Lowes K, Leuchowius KJ. Colorectal cancer cell line proteomes are representative of primary tumors and predict drug sensitivity. *Gastroenterology*. 2017 Oct 1;153(4):1082-95.
32. Xie B, Zhao R, Bai B, Wu Y, Xu Y, Lu S, Fang Y,

Wang Z, Maswikiti EP, Zhou X, Pan H. Identification of key tumorigenesis related genes and their microRNAs in colon cancer. *Oncology Reports*. 2018 Dec 1;40(6):3551-60.

33. Liu X, Gan L, Zhang J. miR-543 inhibites cervical cancer growth and metastasis by targeting TRPM7. *Chemico-biological Interactions*. 2019 Apr 1;302:83-92.

34. Haga CL, Phinney DG. MicroRNAs in the imprinted DLK1-DIO3 region repress the epithelial-to-mesenchymal transition by targeting the TWIST1 protein signaling network. *Journal of Biological Chemistry*. 2012 Dec 14;287(51):42695-707.

35. Zhao Z, Zhang M, Duan X, Chen Y, Li E, Luo L, Wu W, Peng Z, Qiu H, Zeng G. TRPM7 Regulates AKT/FOXO1-Dependent Tumor Growth and Is an Independent Prognostic Indicator in Renal Cell Carcinoma. *Molecular Cancer Research*. 2018 Jun 1;16(6):1013-23.

36. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA: A Cancer Journal for Clinicians*. 2016 Mar;66(2):115-32.

37. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *New England Journal of Medicine*. 1996 Sep 19;335(12):865-75.

38. Brower JV, Clark PA, Lyon W, Kuo JS. MicroRNAs in cancer: Glioblastoma and glioblastoma cancer stem cells. *Neurochemistry International*. 2014 Nov 1;77:68-77.

39. Henriksen M, Johnsen KB, Olesen P, Pilgaard L, Duroux M. MicroRNA expression signatures and their correlation with clinicopathological features in glioblastoma multiforme. *Neuromolecular Medicine*. 2014 Sep 1;16(3):565-77.

40. Henriksen M, Johnsen KB, Olesen P, Pilgaard L, Duroux M. MicroRNA expression signatures and their correlation with clinicopathological features in glioblastoma multiforme. *Neuromolecular Medicine*. 2014 Sep 1;16(3):565-77.

41. Marziali G, Buccarelli M, Giuliani A, Ilari R, Grande S, Palma A, D'Alessandris QG, Martini M, Biffoni M, Pallini R, Ricci-Vitiani L. A three-microRNA signature identifies two subtypes of glioblastoma patients with different clinical outcomes. *Molecular oncology*. 2017 Sep;11(9):1115-29.

42. Gomez GG, Volinia S, Croce CM, Zanca C, Li M, Emmett R, Gutmann DH, Brennan CW, Furnari FB, Cavenee WK. Suppression of microRNA-9 by mutant EGFR signaling upregulates FOXP1 to enhance glioblastoma tumorigenicity. *Cancer Research*. 2014 Mar 1;74(5):1429-39.

43. He DX, Gu XT, Jiang L, Jin J, Ma X. A methylation-based regulatory network for microRNA 320a in chemoresistant breast cancer. *Molecular Pharmacology*. 2014 Nov 1;86(5):536-47.

44. Mu W, Hu C, Zhang H, Qu Z, Cen J, Qiu Z, Li C, Ren H, Li Y, He X, Shi X. miR-27b synergizes with anticancer drugs via p53 activation and CYP1B1 suppression. *Cell Research*. 2015 Apr;25(4):477-95.

45. Chakraborty S, Mazumdar M, Mukherjee S, Bhattacharjee P, Adhikary A, Manna A, Chakraborty S, Khan P, Sen A, Das T. Restoration of p53/miR-34a regulatory axis decreases survival advantage and ensures Bax-dependent apoptosis of non-small cell lung carcinoma cells. *FEBS Letters*. 2014 Feb 14;588(4):549-59.

46. Melo SA, Esteller M. Dysregulation of microRNAs in cancer: playing with fire. *FEBS Letters*. 2011 Jul 7;585(13):2087-99.

47. Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis*. 2013 Jan 1;34(1):48-57.

48. Almasi S, Kennedy BE, El-Aghil M, Sterea AM, Gujar S, Partida-Sánchez S, El Hiani Y. TRPM2 channel-mediated regulation of autophagy maintains mitochondrial function and promotes gastric cancer cell survival via the JNK-signaling pathway. *Journal of Biological Chemistry*. 2018 Mar 9;293(10):3637-50.

49. Mao K, Zhang J, He C, Xu K, Liu J, Sun J, Wu G, Tan C, Zeng Y, Wang J, Xiao Z. Restoration of miR-193b sensitizes Hepatitis B virus-associated hepatocellular carcinoma to sorafenib. *Cancer Letters*. 2014 Oct 1;352(2):245-52.

50. Scheau C, Badarau IA, Caruntu C, Mihai GL, Didilescu AC, Constantin C, Neagu M. Capsaicin: effects on the pathogenesis of hepatocellular carcinoma. *Molecules*. 2019 Jan;24(13):2350.