MicroRNA --- implications for cancer

miRNA	Dysregulation	Function	Validated targets	Oncogene (ONC) or tumour suppressor (TS)	Refs
Let-7 (a, b, c, d, e, f, g,* and *i)	Loss in lung and breast cancer and in various solid and haematopoietic malignancies	Induces apopotosis and inhibits tumorigenesis	RAS, MYC, and DNMTs	TS	(Johnson, 2007; Johnson, et al., 2005; Lee and Dutta, 2007; Sampson, et al., 2007)
miR-15a* and *miR-16-1	Loss in CLL, prostate cancer and multiple myeloma	Induces apoptosis and inhibits tumorigenesis	BCL2, WT1, RAB9B and MAGE83	TS	(Calin, 2002; Calin, et al., 2008; Calin, et al., 2005; Cimmino, et al., 2005)
miR-17-5p				ONC	
miR-17-92* cluster *(miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1,* and *miR-92a-1)	Upregulated in lymphomas and in breast, lung, colon, stomach, and pancreatic cancers	Induces proliferation	E2F1, BIM, and PTEN	ONC	(Mendell, 2008; Ventura, et al., 2008; Volinia, et al., 2006; Xiao, et al., 2008)
miR-21	Upregulated in glioblastomas, AML (11q23), aggressive CLL and breast, colon, pancreatic, lung, prostate, liver, and stomach cancers	Inhibits apoptosis and increases tumorigenicity	PTEN, PDCD4, TPM1, and TIMP3	ONC	(Ciafr, et al., 2005; Fanyin, et al., 2007; Garzon, et al., 2008; He, 2005; Iorio, et al., 2005)
***miR-29 (a, b,* and**	Loss in aggressive CLL, AML	Induces apoptosis and	TCL1, MCL1, and	TS	(Calin, et al.,

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c)	(11q23), MDS lung and breast cancers and cholangocarcinoma	inhibits tumorigenicity. Reactivates silenced tumour suppressor genes	DNMTs		2005; Fabbri, et al., 2007; Mott, et al., 2007; Pekarsky, et al., 2006)
miR-30c		Expression of miR-30c was validated in human HL-60 leukemia cells			(Kasashima, et al., 2004)
miR-34	Loss in pancreatic, colon, breast, and liver cancers	Induces apoptosis	CDK4, CDK6, cyclin E2, EZF3, and MET	TS	(Chang, et al., 2007; He, et al., 2007; Raver-Shapira, et al., 2007)
miR-103		Well-differentiated pancreatic endocrine carcinoma			(Roldo, et al., 2006)
miR-141		Human microRNA-141 (miR-141), a member of the miR-200 family, has been reported to be associated with various human malignancies. miR-141 may be involved in the development of gastric cancer through its inhibitory effect on cell proliferation.			(Du, et al., 2009)
miR-143		Michael et al. subsequently verified expression of miR-143 in human, and			(Michael, et al., 2003)

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		demonstrated significantly reduced levels of the miRNA in precancerous and neoplastic colorectal tissue [2]. miR-143 cloned in [3] has a 1 nt 3' extension (A), which is incompatible with the genome sequence.			
miR-145	Loss in breast cancer	Inhibits proliferation and induces apoptosis of breast cancer cells	ERG	TS	(Iorio, et al., 2005)
miR-146b					(He, et al., 2005)
miR-155	Upregulated in aggressive CLL, BUrkitt's lymphoma and lung, breast and colon cancers	Induces cell proliferation and leukaemia or lymphoma in mice	MAF and SHIP1	ONC	(Costinean, et al., 2006; Eis, et al., 2005)
miR-181(a, b,* and *b1)		Glioblastoma, PTC			(Ciafr, et al., 2005)
miR-199a		Ovary, Cervical SSC			(Iorio, et al., 2007)
miR-200 (a, b, c)		EMT	ZEB1,ZEB2		(Gregory, et al., 2008; Korpal, et al., 2008; Park, et al., 2008)
miR-204		ALL			(Zanette, et al., 2007)
miR-205		EMT			(Gregory, et al., 2008)
miR-221* and *miR-	Loss in erythroblastic leukaemia	Inhibits proliferation in	KIT	TS	(Felli, et al.,

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222		erythroblasts			2005)
miR-221 **and** ***miR-222***	Overexpression in aggressive CLL, thyroid carcinoma, and hepatocellular carcinoma	Promotes cell proliferation and inhibits apoptosis in various solid malignancies	P27, p57, PTEN, and TIMP3	ONC	(Fornari, et al., 2008; Garofalo, et al., 2009; le Sage, et al., 2007)
miR-331		ALL, CLL			(Zanette, et al., 2007)
miR-372 **and** ***miR-373***	Upregulated in testicular tumours	Promotes tumorigenicity in cooperation with RAS	LATS2	ONC	(Voorhoeve, et al., 2006)

Reference

Calin, G. (2002) Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia, *Proc Natl Acad Sci USA*, **99**, 15524 - 15529.

Calin, G.A., Cimmino, A., Fabbri, M., Ferracin, M., Wojcik, S.E., Shimizu, M., Taccioli, C., Zanesi, N., Garzon, R., Aqeilan, R.I., Alder, H., Volinia, S., Rassenti, L., Liu, X., Liu, C.-g., Kipps, T.J., Negrini, M. and Croce, C.M. (2008) MiR-15a and miR-16-1 cluster functions in human leukemia, *Proceedings of the National Academy of Sciences*, **105**, 5166-5171.

Calin, G.A., Ferracin, M., Cimmino, A., Di Leva, G., Shimizu, M., Wojcik, S.E., Iorio, M.V., Visone, R., Sever, N.I., Fabbri, M., Iuliano, R., Palumbo, T., Pichiorri, F., Roldo, C., Garzon, R., Sevignani, C., Rassenti, L., Alder, H., Volinia, S., Liu, C.-g., Kipps, T.J., Negrini, M. and Croce, C.M. (2005) A MicroRNA Signature Associated with Prognosis and Progression in Chronic Lymphocytic Leukemia, *N Engl J Med*, **353**, 1793-1801.

Chang, T.-C., Wentzel, E.A., Kent, O.A., Ramachandran, K., Mullendore, M., Lee, K.H., Feldmann, G., Yamakuchi, M., Ferlito, M., Lowenstein, C.J., Arking, D.E., Beer, M.A., Maitra, A. and Mendell, J.T. (2007) Transactivation of miR-34a by p53 Broadly Influences Gene Expression and Promotes Apoptosis, **26**, 745-752.

Ciafr, S.A., Galardi, S., Mangiola, A., Ferracin, M., Liu, C.G., Sabatino, G., Negrini, M., Maira, G., Croce, C.M. and Farace, M.G. (2005) Extensive modulation of a set of microRNAs in primary glioblastoma, *Biochemical and Biophysical Research Communications*, **334**, 1351-1358.

Cimmino, A., Calin, G.A., Fabbri, M., Iorio, M.V., Ferracin, M., Shimizu, M., Wojcik, S.E., Aqeilan, R.I., Zupo, S., Dono, M., Rassenti, L., Alder, H., Volinia, S., Liu, C.-g., Kipps, T.J., Negrini, M. and Croce, C.M. (2005) miR-15 and miR-16 induce apoptosis by targeting BCL2, *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 13944-13949.
Costinean, S., Zanesi, N., Pekarsky, Y., Tili, E., Volinia, S., Heerema, N. and Croce, C.M. (2006) Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in Eu-miR155 transgenic mice, **103**, 7024-7029.
Du, Y., Xu, Y., Ding, L., Yao, H., Yu, H., Zhou, T. and Si, J. (2009) Down-regulation of miR-141 in gastric cancer and its involvement in cell growth, *Journal of Gastroenterology*, **44**, 556-561.
Eis, P.S., Tam, W., Sun, L., Chadburn, A., Li, Z., Gomez, M.F., Lund, E. and Dahlberg, J.E. (2005) Accumulation of miR-155 and BIC RNA in human B cell lymphomas, *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 3627-3632.
Fabbri, M., Garzon, R., Cimmino, A., Liu, Z., Zanesi, N., Callegari, E., Liu, S., Alder, H., Costinean, S., Fernandez-Cymering, C., Volinia, S., Guler, G., Morrison, C.D., Chan, K.K., Marcucci, G., Calin, G.A., Huebner, K. and Croce, C.M. (2007) MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B, *Proceedings of the National Academy of Sciences*, **104**, 15805-15810.
Fanyin, M., Roger, H., Hania, W., Kalpana, G., Samson, T.J. and Tushar, P. (2007) MicroRNA-21 Regulates Expression of the PTEN Tumor Suppressor Gene in Human Hepatocellular Cancer, *Gastroenterology*, **133**, 647-658.
Felli, N., Fontana, L., Pelosi, E., Botta, R., Bonci, D., Facchiano, F., Liuzzi, F., Lulli, V., Morsilli, O., Santoro, S., Valtieri, M., Calin, G.A., Liu, C.-G., Sorrentino, A., Croce, C.M. and Peschle, C. (2005) MicroRNAs 221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via kit receptor down-modulation, *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 18081-18086.
Fornari, F., Gramantieri, L., Ferracin, M., Veronese, A., Sabbioni, S., Calin, G.A., Grazi, G.L., Giovannini, C., Croce, C.M., Bolondi, L. and Negrini, M. (2008) MiR-221 controls CDKN1C/p57 and CDKN1B/p27 expression in human hepatocellular carcinoma, *Oncogene*, **27**, 5651-5661.
Garofalo, M., Di Leva, G., Romano, G., Nuovo, G., Suh, S.-S., Ngankeu, A., Taccioli, C., Pichiorri, F., Alder, H., Secchiero, P., Gasparini, P., Gonelli, A., Costinean, S., Acunzo, M., Condorelli, G. and Croce, C.M. (2009) miR-221&222 Regulate TRAIL Resistance and Enhance Tumorigenicity through PTEN and TIMP3 Downregulation, **16**, 498-509.
Garzon, R., Volinia, S., Liu, C.-G., Fernandez-Cymering, C., Palumbo, T., Pichiorri, F., Fabbri, M., Coombes, K., Alder, H., Nakamura, T., Flomenberg, N., Marcucci, G., Calin, G.A., Kornblau, S.M., Kantarjian, H., Bloomfield, C.D., Andreeff, M. and Croce, C.M. (2008) MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia, *Blood*, **111**, 3183-3189.
Gregory, P.A., Bert, A.G., Paterson, E.L., Barry, S.C., Tsykin, A., Farshid, G., Vadas, M.A., Khew-Goodall, Y. and Goodall, G.J. (2008) The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, *Nat Cell Biol*, **10**, 593-601.
He, H., Jazdzewski, K., Li, W., Liyanarachchi, S., Nagy, R., Volinia, S., Calin, G.A., Liu, C.-g., Franssila, K., Suster, S., Kloos, R.T., Croce, C.M. and de la Chapelle, A. (2005) The role of microRNA genes in papillary thyroid carcinoma, *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 19075-19080.
He, L. (2005) A microRNA polycistron as a potential human oncogene, *Nature*, **435**, 828 - 833.

He, L., He, X., Lim, L.P., de Stanchina, E., Xuan, Z., Liang, Y., Xue, W., Zender, L., Magnus, J., Ridzon, D., Jackson, A.L., Linsley, P.S., Chen, C., Lowe, S.W., Cleary, M.A. and Hannon, G.J. (2007) A microRNA component of the p53 tumour suppressor network, *Nature*, **447**, 1130-1134.
Iorio, M.V., Ferracin, M., Liu, C.-G., Veronese, A., Spizzo, R., Sabbioni, S., Magri, E., Pedriali, M., Fabbri, M., Campiglio, M., Menard, S., Palazzo, J.P., Rosenberg, A., Musiani, P., Volinia, S., Nenci, I., Calin, G.A., Querzoli, P., Negrini, M. and Croce, C.M. (2005) MicroRNA Gene Expression Deregulation in Human Breast Cancer, *Cancer Res*, **65**, 7065-7070.
Iorio, M.V., Visone, R., Di Leva, G., Donati, V., Petrocca, F., Casalini, P., Taccioli, C., Volinia, S., Liu, C.-G., Alder, H., Calin, G.A., Menard, S. and Croce, C.M. (2007) MicroRNA Signatures in Human Ovarian Cancer, *Cancer Res*, **67**, 8699-8707.
Johnson, C. (2007) The let-7 microRNA represses cell proliferation, *Cancer Res*, **67**, 7713 - 7722.
Johnson, S.M., Grosshans, H., Shingara, J., Byrom, M., Jarvis, R., Cheng, A., Labourier, E., Reinert, K.L., Brown, D. and Slack, F.J. (2005) RAS Is Regulated by the let-7 MicroRNA Family, **120**, 635-647.
Kasashima, K., Nakamura, Y. and Kozu, T. (2004) Altered expression profiles of microRNAs during TPA-induced differentiation of HL-60 cells, *Biochemical and Biophysical Research Communications*, **322**, 403-410.
Korpal, M., Lee, E.S., Hu, G. and Kang, Y. (2008) The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2, *J. Biol. Chem.*, C800074200.
le Sage, C., Nagel, R., Egan, D.A., Schrier, M., Mesman, E., Mangiola, A., Anile, C., Maira, G., Mercatelli, N., Ciafre, S.A., Farace, M.G. and Agami, R. (2007) Regulation of the p27Kip1 tumor suppressor by miR-221 and miR-222 promotes cancer cell proliferation, *EMBO J*, **26**, 3699-3708.
Lee, Y.S. and Dutta, A. (2007) The tumor suppressor microRNA let-7 represses the HMGA2 oncogene, *Genes & Development*, **21**, 1025-1030.
Mendell, J.T. (2008) miRiad Roles for the miR-17-92 Cluster in Development and Disease, **133**, 217-222.
Michael, M., O'Connor, S., Pellekaan, N., Young, G. and James, R. (2003) Reduced accumulation of specific mi-croRNAs in colorectal neoplasia, *Mol Cancer Res*, **1**, 882 - 891.
Mott, J.L., Kobayashi, S., Bronk, S.F. and Gores, G.J. (2007) mir-29 regulates Mcl-1 protein expression and apoptosis, *Oncogene*, **26**, 6133-6140.
Park, S.-M., Gaur, A.B., Lengyel, E. and Peter, M.E. (2008) The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2, *Genes & Development*, **22**, 894-907.
Pekarsky, Y., Santanam, U., Cimmino, A., Palamarchuk, A., Efanov, A., Maximov, V., Volinia, S., Alder, H., Liu, C.-G., Rassenti, L., Calin, G.A., Hagan, J.P., Kipps, T. and Croce, C.M. (2006) Tcl1 Expression in Chronic Lymphocytic Leukemia Is Regulated by miR-29 and miR-181, *Cancer Res*, **66**, 11590-11593.
Raver-Shapira, N., Marciano, E., Meiri, E., Spector, Y., Rosenfeld, N., Moskovits, N., Bentwich, Z. and Oren, M. (2007) Transcriptional Activation of miR-34a Contributes to p53-Mediated Apoptosis, **26**, 731-743.
Roldo, C., Missiaglia, E., Hagan, J.P., Falconi, M., Capelli, P., Bersani, S., Calin, G.A., Volinia, S., Liu, C.-G., Scarpa, A. and Croce, C.M. (2006) MicroRNA Expression Abnormalities in Pancreatic Endocrine and Acinar Tumors Are Associated With Distinctive Pathologic Features and Clinical Behavior, *J Clin Oncol*, **24**, 4677-4684.

Sampson, V.B., Rong, N.H., Han, J., Yang, Q., Aris, V., Soteropoulos, P., Petrelli, N.J., Dunn, S.P. and Krueger, L.J. (2007) MicroRNA Let-7a Down-regulates MYC and Reverts MYC-Induced Growth in Burkitt Lymphoma Cells, *Cancer Res*, **67**, 9762-9770.
Ventura, A., Young, A.G., Winslow, M.M., Lintault, L., Meissner, A., Erkeland, S.J., Newman, J., Bronson, R.T., Crowley, D., Stone, J.R., Jaenisch, R., Sharp, P.A. and Jacks, T. (2008) Targeted Deletion Reveals Essential and Overlapping Functions of the miR-17<92 Family of miRNA Clusters, **132**, 875-886.
Volinia, S., Calin, G.A., Liu, C.-G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R.L., Yanaihara, N., Lanza, G., Scarpa, A., Vecchione, A., Negrini, M., Harris, C.C. and Croce, C.M. (2006) A microRNA expression signature of human solid tumors defines cancer gene targets, *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 2257-2261.
Voorhoeve, P.M., le Sage, C., Schrier, M., Gillis, A.J.M., Stoop, H., Nagel, R., Liu, Y.-P., van Duijse, J., Drost, J., Griekspoor, A., Zlotorynski, E., Yabuta, N., De Vita, G., Nojima, H., Looijenga, L.H.J. and Agami, R. (2006) A Genetic Screen Implicates miRNA-372 and miRNA-373 As Oncogenes in Testicular Germ Cell Tumors, **124**, 1169-1181.
Xiao, C., Srinivasan, L., Calado, D.P., Patterson, H.C., Zhang, B., Wang, J., Henderson, J.M., Kutok, J.L. and Rajewsky, K. (2008) Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes, *Nat Immunol*, **9**, 405-414.
Zanette, D.L., Rivadavia, F., Molfetta, G.A., Barbuzano, F.G., Proto-Siqueira, R., Falcao, R.P., Zago, M.A. and Silva-Jr, W.A. (2007) miRNA expression profiles in chronic lymphocytic and acute lymphocytic leukemia, *Brazilian Journal of Medical and Biological Research*, **40**, 1435-1440.