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Let-7, miR-125, miR-205, and miR-296 are prospective therapeutic agents in breast cancer molecular medicine

Research Article

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Abbreviations: Acute lymphoblastic leukemia, (AL); Breast cancer, (BC); Burkitts lymphoma; (BL); Estrogen receptor, (ER); microRNA let-7, (let-7); Loss of heterozygocity, (LOH); micro RNAs, (miRs); Replication factors, (RCFs)

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Summary

Increasing evidences in recent years demonstrate that several biological processes and disease pathogenesis are regulated by micro RNAs (miRs) and restoration of normal miR activity can be new way of treating cancers. Several genetic alterations and deregulation of miRs have been reported in breast cancer. Similarly, side effects of conventional chemotherapeutic drugs are well known. In this research, using a broad bioinformatics approach we have identified critical disease pathways and drug targets in female breast cancer. Replacement therapy with let-7 is already under clinical trails for lung cancer. Here we have shown that restoration of let-7 along with miR-125 or miR-205 or miR-296 can potentially inhibit all critical disease pathways involved in breast cancer irrespective of patient specific molecular profile. Results also suggest that these miRs might be the future therapeutic agents in breast cancer molecular medicine with out side effects.

I. Introduction

A. miRs regulate biological processes and diseases

microRNAs (miRs) are endogenous non-coding pool of small RNA molecules of 20-24 nucleotides in length (Ambros, 2001; Carrington and Ambros, 2003; Bartel, 2004) regulate gene expression by cleaving target mRNAs or by complementarity base pairing at 3□ UTRs inhibiting translation of target mRNAs (Lai, 2002; de Moor et al, 2005; Robins and Press, 2005; Stark et al, 2005; Sun et al, 2005) and thus regulate biological processes. The total number of miRs may be more than 1% of the total protein coding genes in different species (Lai et al, 2003; Lim et al, 2003; Lim et al, 2003) and according to computational prediction around 30% of protein-coding genes may be targeted by miRs (Berezikov et al, 2005; Lewis et al, 2005). miRs have been found to involved in several biological processes. For example, miR-9 in insulin secretion (Plaisance et al, 2006), miR-122 in lipid metabolism (Esau et al, 2006), miR-143 and miR-206 and in adiposity and muscle differentiation (Esau et al, 2004; Kim et al, 2006), miR-1 and miR-133 ES differentiation, mesoderm formation, and heart development and physiology (Chen et al, 2006; Zhao et al, 2007; Ivey et al, 2008), miR-208 in cardiomyocyte hypertrophy (van et al, 2007), miR-34a, miR-125b, and miR-128 in apoptosis (Lukiw and Pogue, 2007; Tarasov et al, 2007), miR-34a, miR-34b, miR-34c, miR-93, and miR-214 in aging (Kumamoto et al, 2008; Maes et al, 2008), miR-181 in B-cell progenitor determination and lineage differentiation and T-cell receptor signaling (Chen et al, 2004), and miR-155 in antigen presentation (Rodriguez et al, 2007). Several reports suggest that miRs are also involved in various pathological conditions. For example, miR-203 and miR-146 in inflammatory diseases, miR-196 and miR-122 in anti-viral response (Jopling et al, 2006; Sonkoly et al, 2008), miR-29a/b-1, miR-107 in Alzheimer's disease (Hébert et al, 2008; Wang et al, 2008), miR-433 variation

in Parkinson disease (Wang et al, 2008), miR-19a and miR-21 in Cowden syndrome (Pezzolesi et al, 2008), miR-99a, let-7c, miR-125b-2, miR-155, and miR-802 overexpression in down syndrome (Kuhn et al, 2008), and miR-17-92 in autoimmune diseases (Xiao et al, 2008).

B. miRs and cancer

52.5% human miR genes are located at chromosomal locus those are frequently altered in human cancers (Calin et al, 2004). Increasing evidences suggest that miRs are directly involved in cancer pathogenesis and thus their expression profiles are useful for cancer diagnosis, prognosis, staging, and treatment. miRs are reported to act as oncogenes (oncomirs) (Hayashita et al, 2005; He et al, 2005; O'Donnell et al, 2005; Hammond, 2006; Cho, 2007) and tumor suppressor genes (Ambros, 2004; Bartel, 2004; Miska et al, 2004; Thomson et al, 2004; Tavazoie et al, 2008). Metastatic and angiogenic properties of miRs are also in report (Ma et al, 2007; Huang et al, 2008; Negrini and Calin, 2008; Tavazoie et al, 2008; Urbich et al, 2008). Recent studies have revealed that miRs are frequently deregulated and regulate pathological events in most common cancers. miR deregulation have been reported in breast cancer (Iorio et al, 2005; Hossain et al, 2006; Hurteau et al, 2007; Lowery et al, 2007; Ma et al, 2007; Scott et al, 2007; Sempere et al, 2007; Si et al, 2007; Yu et al, 2007; Zhu et al, 2007; Cissell et al, 2008; Frankel et al, 2008; Huang et al, 2008; Lehmann et al, 2008; Tavazoie et al, 2008), colorectal cancer (Michael et al, 2003; Akao et al, 2006; Bandrés et al, 2006; Xi et al, 2006; Lanza et al, 2007; Nakagawa et al, 2007; Slaby et al, 2007; Asangani et al, 2008; Grady et al, 2008; Schetter et al, 2008), glioblastoma (Chan et al, 2005; Ciafre et al, 2005; Gillies et al, 2007; Kefas et al, 2008), hepatocellular carcinoma (Kutay et al, 2006; Murakami et al, 2006; Gramantieri et al, 2007; Meng et al, 2007; Huang et al, 2008; Jiang et al, 2008; Varnholt et al, 2008; Wang et al, 2008; Wong et al, 2008; Yang et al, 2008), lung cancer (Lewis et al, 2003; Takamizawa et al, 2004; Hayashita et al, 2005; Fabbri et al, 2007; Hurteau et al, 2007; Inamura et al, 2007; Matsubara et al, 2007; Hu et al, 2008; Ventura et al, 2008; Weiss et al, 2008), lymphomas (Metzler et al, 2004; Cimmino et al, 2005; Eis et al, 2005; He et al, 2005; Kluiver et al, 2005; Akao et al, 2007; Lawrie et al, 2007; Lum et al, 2007; Mi et al, 2007; Motsch et al, 2007; Rinaldi et al, 2007; Sampson et al, 2007; Xiao et al, 2008; Bueno et al, 2008; Faber et al, 2008; Rai et al, 2008; Lawrie et al, 2008; Navarro et al, 2008; Roehle et al, 2008), papillary thyroid carcinoma (PTC) (He et al, 2005; Weber et al, 2006; Tetzlaff et al, 2007; Visone et al, 2007; Jazdzewski et al, 2008; Nikiforova et al, 2008; Mitomo et al, 2008; Takakura et al, 2008), testicular germ cell cancer (Voorhoeve et al, 2006), and several other cancers (**Table 1**). High throughput miR expression data show that several miRs are differentially expressed in various cancers including breast cancer (Nam et al, 2008) (**Table 2**).

Table 1. miR deregulation in various cancers.

Cancer	Upregulated miRs	Downregulated miRs	References
Acute lymphoblastic leukemia	miR-155		Costinean et al, 2006
		miR-203	Bueno et al, 2008
	miR-128a and miR-128b	let-7b and miR-223	Mi et al, 2007
Anaplastic thyroid cancer		miR-30d, miR-125b, miR-26a, and miR-30a-5p	Visone et al, 2007
Diffuse large B cell lymphoma	miR-155		Metzler et al, 2004; Eis et al, 2005
	miR-21		Lawrie et al, 2007
		miR-15a	Eis et al, 2005
	miR-155, miR-210 and miR-21		Lawrie et al, 2008
B-cell chronic lymphocytic leukemia		miR-15a, miR-15b, miR-16-1, and miR-16-2	Calin et al, 2002
		miR-15a and miR-16-1	Cimmino et al, 2005
	miR-150, mir-155 and mir-21	miR-222, miR-92a-1, miR-92a-2, miR-15a, and miR-16	Fulci et al, 2007
	miR-155		Metzler et al, 2004
		miR-143 and miR-145.	Akao et al, 2007
Burkitts lymphoma	miR-155		Metzler et al, 2004
	miR-146a and miR-155		Motsch et al, 2007
		let-7a	Sampson et al, 2007
		miR-143 and miR-145	Akao et al, 2007
Breast cancer		miR-125b, miR-145, miR-21, and miR-155	Iorio et al, 2005
		miR-17-5p	Hossain et al, 2006
		let-7a	Yu et al, 2007
		miR-126 and miR-335	Tavazoie et al, 2008
	miR21	miR-145, miR-205 and let-7a	Sempere et al, 2007
		miR-9-1, miR-124a3, miR-148, miR-152, and miR-663	Lehmann et al, 2008
	miR21		Si et al, 2007
	miR-373 and miR-520c		Huang et al, 2008

Cervical cancer	miR-127 and miR-199a		Lee et al, 2008
		miR-218	Martinez et al, 2008
	miR-21	miR-143	Lui et al, 2007
Chronic mylogenous leukemia		miR-203	Bueno et al, 2008
Colorectal cancer	miR-21		Schetter et al, 2008
	miR-21 and miR-31	miR-143 and miR-145.	Slaby et al, 2008
		miR-7-3	Jiang et al, 2005
	miR-31, miR-96, miR-135b, and miR-183.	miR-133b and miR-145.	Bandrés et al, 2006
	miR-15b, miR-181b, miR-191, and miR-200c		Xi et al, 2006
	miR-17-92		Lanza et al, 2007
		miR-143 and miR-145	Michael et al, 2003; Akao et al, 2006
		let-7	Akao et al, 2006
		miR-342	Grady et al, 2008
Cholangiocarcinoma	miR-21, miR-141, and miR-200b		Meng et al, 2006
Follicular thyroid carcinoma	miR-197 and miR-346		Weber et al, 2006
Glioblastoma	miR-221	miR-181a, miR-181b, and miR-181c	Ciafre et al, 2005
	miR-21		Chan et al, 2005
	miR221 and miR-222		Gillies et al, 2007
		miR-7	Kefas et al, 2008
Head and neck cancer	miR-21 and miR-205		Tran et al, 2007
Hodgkin's lymphoma	miR-155		Kluiver et al, 2005
		miR-96, miR-128a, and miR-128b	Navarro et al, 2008
Insulinomas	miR-204		Roldo et al, 2006
Hepatocellular carcinoma		miR-122	Kutay et al, 2006
		miR-122a	Gramantieri et al, 2007
	miR-21		Meng et al, 2007
	miR-199a, miR-21, and miR-301		Jiang et al, 2008
	miR-122, miR-100, and miR-10a	miR-198 and miR-145	Varnholt et al, 2008
	miR-224		Wang et al, 2008
	miR-23a-27a		Huang S et al, 2008
		miR-223	Wong et al, 2008
Lung cancer	miR-17-92, miR-19a, miR-20, miR-106a, and miR-106b		Hayashita et al, 2005
		miR-200c	Hurteau et al, 2007
		miR-128b	Weiss et al, 2008
		let-7	Takamizawa et al, 2004 Inamura K 2007
		let-7a-3	Brueckner et al, 2007
Mantle cell lymphoma	miR-17-92		Rinaldi et al, 2007
Nasopharyngeal cancer		miR-29c	Sengupta et al, 2008
Neuroblastoma		miR-34a	Welch et al, 2007; Cole et al, 2008
Osteosarcoma	miR-165, miR-166, miR-17, miR-20a, and miR-21		Gao et al, 2007
Ovary cancer	miR-200a, miR-141, miR-200c, miR-200b, miR-21, miR-203, and miR-205	miR-199a, miR-140, miR-145 and miR-125b1	Iorio et al, 2007
	miR-214		Yang et al, 2008
		let-7a-3	Lu et al, 2007
Pancreatic cancer	miR-155, miR-21, miR-221, mirR-222, miR-301a, miR-301b, miR-376a-1 and miR-376a-2		Lee et al, 2007
	miR-196a-2		Bloomston et al, 2007
	miR-155		Gironella et a, 2007

Prostate cancer		let-7c	Jiang et al, 2005
		miR-125b-1and miR-125b-2	Lee et al, 2005
Testicular germ-cell tumors	miR-372 and miR-373		Voorhoeve et al, 2006
T-cell lymphoma	miR-363		Lum et al, 2007
Papillary thyroid carcinoma	miR-221, miR-222, and miR-146		He et al, 2005
	miR-221, miR-222, and miR-181b		Pallante et al, 2006
		miR-138	Mitomo et al, 2008
		miR-146a	Jazdzewski et al, 2008
	miR-187, miR-221, miR-222, miR-146b, miR-155, miR-224, and miR-197		Nikiforova et al, 2008

Table 2. miRGator microarray analysis of deregulated miRs in breast (normal vs cancer).

Upregulated miRs (63)	Downregulated miRs (86)
miR-323, miR-324-3p, miR-326, miR-328, miR-331, miR-338, miR-339, miR-340, miR-342, miR-335, miR-129, miR-148a, miR-218, miR-130a, miR-199b, miR-1, miR-197, miR-150, miR-23b, miR-100, miR-99a, let-7b, miR-191, miR-194, miR-204, miR-133a, miR-30a-3p, miR-21, miR-154, miR-10b, miR-223, miR-28, miR-190, miR-145, and miR-134.	miR-152, miR-29a, miR-16, miR-34c, miR-26a, miR-33, let-7d, miR-182*, miR-199a, miR-128b, miR-200a, miR-184, miR-185, let-7f, miR-193, miR-188, miR-130b, miR-219, miR-206, miR-216, miR-217, miR-181c, miR-138, miR-107, miR-301, miR-302a, miR-31, miR-125a, miR-106b, let-7a, miR-93, miR-30e, miR-30a-5p, miR-324-5p, miR-224, miR-320, miR-137, miR-103, miR-99b, miR-15b, miR-210, miR-136, miR-24, miR-203, miR-212, miR-186, miR-27a, miR-147, miR-199a*, miR-101, let-7g, miR-105, miR-19b, miR-30d, let-7e, miR-211, let-7c, miR-17-5p, miR-128a, miR-148b, miR-149, miR-299, miR-155, miR-29b, miR-127, miR-187, miR-192, miR-23a, miR-19a, miR-26b, miR-208, miR-135a, miR-125b, miR-29c, miR-124a, miR-106a, miR-126, miR-7, miR-95, miR-146, miR-27b, miR-20, miR-32, miR-183, miR-15a, miR-140, miR-143, miR-296, miR-92, miR-144, miR-215, miR-34a, miR-139, miR-34b, miR-142-3p, miR-221, miR-30b, miR-141, miR-135b, miR-181a, let-7i, miR-222, miR-200b, miR-96, miR-153, miR-122a, miR-98, miR-142-5p, miR-9*, miR-181b, miR-18, miR-9, and miR-200c.

C. Mechanism of miRs and their targets

The mechanisms of gene regulation by miR (Lai, 2002; de Moor et al, 2005; Stark et al, 2005; Sun et al, 2005; Du and Zamore, 2007; Pillai et al, 2007; Standart and Jackson, 2007), their mechanisms of growth regulation (Lewis et al, 2003; O'Donnell et al, 2005; Ma et al, 2007; Esquela-Kerscher et al, 2008; Kumar et al, 2008; Tavazoie et al, 2008), and experimentally identification and computational predictions of their target mRNAs are also under extensive study (Bentwich, 2005; Rajewsky, 2006; Doran and Strauss, 2007; Maziere and Enright, 2007; Kuhn et al, 2008). Few of such miR targets are described in (**Table 3**). Recent studies have also shown that restoration of key downregulated miRs (Takamizawa et al, 2004; Esquela-Kerscher et al, 2008; Grady et al, 2008) and inhibition of oncomirs (Corsten et al, 2007; Matsubara et al, 2007; Si et al, 2007; Cissell et al, 2008) in respective cancers can inhibit cancer growth and restore normal condition, which indicate the potential therapeutic applications of miRs in various cancers.

D. Female breast cancer biomarkers and drugs

Breast cancer is one of the most common cancers with highest cancer specific death rate in women worldwide (National Cancer Institute's SEER Program database http://seer.cancer.gov/statfacts/html/breast.html, Mettlin, 1999; Miller et al, 2008). The tumor biology and epidemiology of breast cancer also varies depending on the race, geographical locations, and several other factors (Amend et al, 2006; Smigal et al, 2006; Li and Daling, 2007; Hausauer et al, 2007). Several genetic alterations and biomarkers have been found to be associated with breast cancer (Ross et al, 2003; Ross et al, 2004; Jain, 2007; McCracken et al, 2007; Levenson and Somers, 2008; Laversin et al, 2008; Marchionni et al, 2008; see breast cancer specific genetic databases also) and several groups of chemotherapeutic drugs such as selective estrogen-receptor modulators (Riggs and Hartmann, 2003; Lewis and Jordan, 2005; Ramona et al, 2007), aromatase inhibitors (Smith and Dowsett, 2003; Jonathan, 2006; Nabholtz and Gligorov, 2006; Herold and Blackwell, 2008) anthracyclines (Hennessy and Pusztai, 2005; von Minckwitz, 2007; Dean-Colomb and Esteva, 2008), and

targeted therapeutics (Gerber, 2008; Higgins and Wolff, 2008; Nahleh, 2008) are commonly used in treatment of breast cancer those are also reported to evoke frequent severe side effects (Jones et al, 2006; Gianni et al, 2007; Moore, 2007; Harris, 2008; Yamada, 2008).

E. Objective

Keeping in mind the hetrogenecity of BC and side effects of conventional therapeutics, based on available data, we tried to construct a universial and common critical disease pathway and drug targets, regardless to the molecular profile of specific BCs. Next we have taken the effort to target those critical components of the constructed pathway with minimum numbers of naturally occurring miRs to block the entire network, which might be a potential therapeutic strategy in breast cancer gene therapy without any side effect.

Table 3. Experimental targets of miRs in different cancers

Cancers	Deregulated miRs	Targets	References
ALL and BL	miR-155	†*BCL6*	Saito et al, 2006
Diffuse large B-cell lymphoma	miR-155	BIC	Eis et al, 2005
		PU1	John et al, 2004
	miR-21	†*PTEN*	Meng et al, 2006
		†*TPM1*	Zhu et al, 2007
B-cell chronic lymphocytic leukemia	miR-15	†*DMTF1*	Kiriakidou et al, 2004
		†*BCL2*	Cimmino et al, 2005
	miR-16	†*CGI-38*	Kiriakidou et al, 2004
		†*BCL2*	Cimmino et al, 2005
	miR-222	†*KIT*	Felli et al, 2005
Breast cancer	miR-520c	CD44	Negrini and Calin, 2008
	miR-10b	HOXD10	Ma et al, 2007
	miR-335	SOX4 and TNC	Tavazoie et al, 2008
	miR-373	CD44	Huang et al, 2008
	miR-17-5p	AIB1	Hossain et al, 2006
	miR-125a and **miR-125a**	**ERBB2** and **ERBB3**	Scott et al, 2007
	miR-21	FAM3C, ACTA2, APAF1, BTG2, FAS, CDKN1A (p21), and SESN1	Frankel et al, 2008
		TPM1	Zhu et al, 2007
	let-7	**H-RAS** and **HMGA2**	Yu et al, 2007
Cervical cancer	miR-17– 92	E2F1	O'Donnell et al, 2005
	miR-127	†*BCL6*	Saito et al, 2006
	miR-143	†*ERK5*	Esau et al, 2004
Chronic mylogenous leukemia	miR-203	BCR-ABL1	Bueno et al, 2008; Faber et al, 2008
Colorectal cancer	miR-143	ERK5	Akao et al, 2006; Nakagawa et al, 2007
	miR 145	IRS1	Shi et al, 2007
	let-7	**RAS** and **MYC**	Akao et al, 2006
	miR-21	PDCD4	Asangani et al, 2008
	miR-133	†*SRF*	Chen et al, 2006
		†*PTBP2*	Boutz et al, 2007
		†*ERG*	Xiao et al, 2007
	miR-145	†*FLJ21308*	Kiriakidou et al, 2004
		†*ERK5*	Esau et al, 2004
Cholangiocarcinoma	miR-141	†*Clock*	Kiriakidou et al, 2004
Hepatocellular cancer	miR-122	†*CAT-1*	Chang et al, 2004
	miR-145	†*FLJ21308*	Kiriakidou et al, 2004
	miR-223	†*NFIA*	Fazi et al, 2005
	let-7	CCNA2, CDC34, DBF4, STK6, STK12, E2F5, CDK8, PALG1-2, LIN28B, DICER1, GMNN, **NRAS,** HMGA2, CDC2, **CDC25A**, CCNB1, CCNE2, CCNF, CCNJ, SKP2, CKS1B, CDC20, CDCA1, CDAC2-8, RRM1-2, CDC6, CDC45L, CTD1, ORC1L, **E2F6**, E2F8, **CHEK**1, BUB1, MAD2L1,	Johnson et al, 2007

		CDC23, FANCD2, **BRCA1, BRCA2,** and SOX9	
Glioblastoma	miR-7	**EGFR** and **AKT**	Kefas et al, 2008
	miR-221,	p27	Gillies et al, 2007
	miR-222	p57	Medina et al, 2008
Lung cancer	**let-7**	**RAS** and **MYC**	Johnson et al, 2005; Kumar et al, 2008
	miR-17–92	MYC	Hayashita et al, 2005
		PTEN and RB2	Lewis et al, 2003
	miR-200c	TCF8	Hurteau et al, 2007
	miR-128b	**EGFR**	Weiss et al, 2008
	miR-29	DNMT3A and DNMT3B	Fabbri et al, 2007
	miR-19a	†*PTEN*	Lewis et al, 2003
	miR-20	†*E2F1*	O'Donnell et al, 2005
	miR-106a	†*RB1*	Volinia et al, 2006
	let-7a	†*NF2*	Meng et al, 2007
	let-7	CCNA2, CDC34, DBF4, STK6, STK12, E2F5, CDK8, PALG1-2, LIN28B, DICER1, GMNN, NRAS, and HMGA2	Johnson et al, 2007
Melanoma	**let-7b**	**Cyclins D1, D3, A,** and **CDK-4**	Schultz et al, 2008
Nasopharyngeal cancer	miR-29	†*TCL1*	Pekarsky et al, 2006
Neuroblastoma	miR-34a	†*E2F3*	Welch et al, 2007
Osteosarcoma	miR-20a	†*TGFBR2*	Volinia et al, 2006
Ovary cancer	miR-140	†*HDAC4*	Tuddenham et al, 2006
Pancreatic cancer	miR-221	†*KIT*	Felli et al, 2005
	miR-222	†*KIT*	Felli et al, 2005
	miR-196	†*HOXA7, HOXC8, HOXD8, and HOXB8*	Yekta et al, 2004
Testicular germ cell cancer	miR-372	LATS2	Voorhoeve et al, 2006
	miR-373	LATS2	Voorhoeve et al, 2006
		†*KIF23, GBAS, C5orf5, C2orf18, PHC2, CD24, NUPL1, MYBL1, HERPUD1, UC7L2, LMNB1, INSIG2, CDK11, MKRN1, TOPK CD83, NCB5OR, RNF149, TNFAIP1, STX11, RELA, STK4, EG1, and RPIA*	Lim et al, 2005
Thyroid cancer	miR-221 miR-222 miR-146	KIT	He et al, 2005; John et al, 2004; Krek et al, 2005; Rehmsmeier et al, 2004

Highlighted miRs are upregulated and non-highlighted are downregulated in respectective cancers. † marked targets and references are taken from TarBase (Sethupathy et al, 2006) (http://www.diana.pcbi.upenn.edu). References taken from TarBase are not given in reference list.

II. Materials and Methods

A. Databases and analysis tools for identification of breast cancer critical disease pathway

Using literature survey databases (Pubmed, Elsevier, Medline) and breast cancer specific three genetic alteration databases [Breast cancer genetic alterations (http://ghr.nlm.nih.gov), Tumor Gene Family of Databases (http://www.tumor-gene.org/Breast/bcgd.html), and SciMedWeb® (http://www.geocities.com/m.lacroix/marqueurs/lismark.htm#A)] we selected several upregulated genes those were verified with microarray data from Hedenfalk and colleagues (Hedenfalk et al. 2001) for hereditary BC for their highest upregulation using BRB ArrayTools- version 3.6.0 (http://linus.nci.nih.gov/BRB-ArrayTools.html). Most frequent upregulated 15 genes and mutated 10 genes were considered for critical disease pathway construction using Osprey-Version 1.0.1 (http://biodata.mshri.on.ca/osprey/servlet/Index), Ingenuity Systems Pathways Analysis-version 5.5 (www.ingenuity.com), and Pathway Architect-version 3.0.1 (www.stratagene.com). Pathways, key nodes, and up and down stream target analysis were done following methods as described by Barh and Das, 2008. The final critical disease pathway was drawn using Cell Illustrator 3.0 (http://www.cellillustrator.com).

B. Identification of cancer associated miRs

PubMed was screened for literatures describing various cancer-related miRs using key words "....cancer micro RNA".

Data obtained from the searches were used for the identification specific miRs and their association with related cancers. Two additional miR databases Argonaute-2 (Shahi et al, 2006) (http://www.ma.uni-heidelberg.de/apps/zmf/argonaute/disease.php) and miRGator (Nam et al, 2008) (http://genome.ewha.ac.kr/miRGator) were also used as reference for identification of cancer associated miRs.

C. Identification of critical disease pathway targeting miRs

Five micro RNA resource and analysis databases were used for this purpose. TarBase (Sethupathy et al, 2006) (http://www.diana.pcbi.upenn.edu/tarbase.html) was used to find the experimentally supported specific miR targets corresponding to specific cancer. miRBase (Griffiths-Jones et al, 2008) (http://microrna.sanger.ac.uk/cgi-bin/targets/v5/search.pl), PicTar (Krek et al, 2005) (http://pictar.bio.nyu.edu/cgi-bin/PicTar_vertebrate.cgi), and TargetScan Release 4.2 (Lewis et al, 2003; Lewis et al, 2005) (http://www.targetscan.org) were used to predict miRs those can target genes involved in BC critical disease pathway. miRanda (John et al, 2004) (http://cbio.mskcc.org/cgi-bin/mirnaviewer/mirnaviewer.pl) was used for identification of common miRs those can act on several targets of our breast cancer critical pathways.

III. Results

A. Breast cancer critical disease pathway and drug targets

3 critical pathways (ER signaling, mitogenic signaling, and DNA repair), similar to male breast cancer critical pathways (Barh and Das, 2008) have been found to interplay in female breast cancer too **(Figure 1)**. All key nodes of the constructed pathway are found to be potential drug targets. Identified key nodes of the entire pathway are EGF, ESR1, ERBB2, JUN, MMP2, PCNA, AKT, VEGF, NF-κB, CCND1, and CDK4.

ER signaling pathway can be disrupted by targeting CYP19A1, ESR1, NF-κB, and MYC. Identified key targets of the growth factor signaling pathway are mainly ERBB2, EGFR, JUN, AKT, β-catenin. EGF and JUN are found to be common upstream drug targets of these two pathways. RB, PCNA, E2F1, and CCND1 can be considered as critical targets in DNA repair critical path. β-catenin and CCND1 seems to be common targets for growth factor signaling and DNA repair pathways. It has been found that common down stream targets of all critical pathways are NF-κB, FOS, MYC, β-catenin, and CCND1.

B. Up and downstream target analysis

Up and downstream analysis of terminal key nodes of the critical pathway shows that one or more transcription factors, cell cycle regulators, components of replication machinery, tumor suppressor genes, and growth factors are downstream targets of several key nodes **(Table-4).** For example, MYC is a down stream target for all three critical pathways and CDC25A, CDK4, eIF-4E, and ERBB2 are downstream targets of MYC. Similarly, for β-catenin, downstream targets are CCND1, FOS, and MYC.

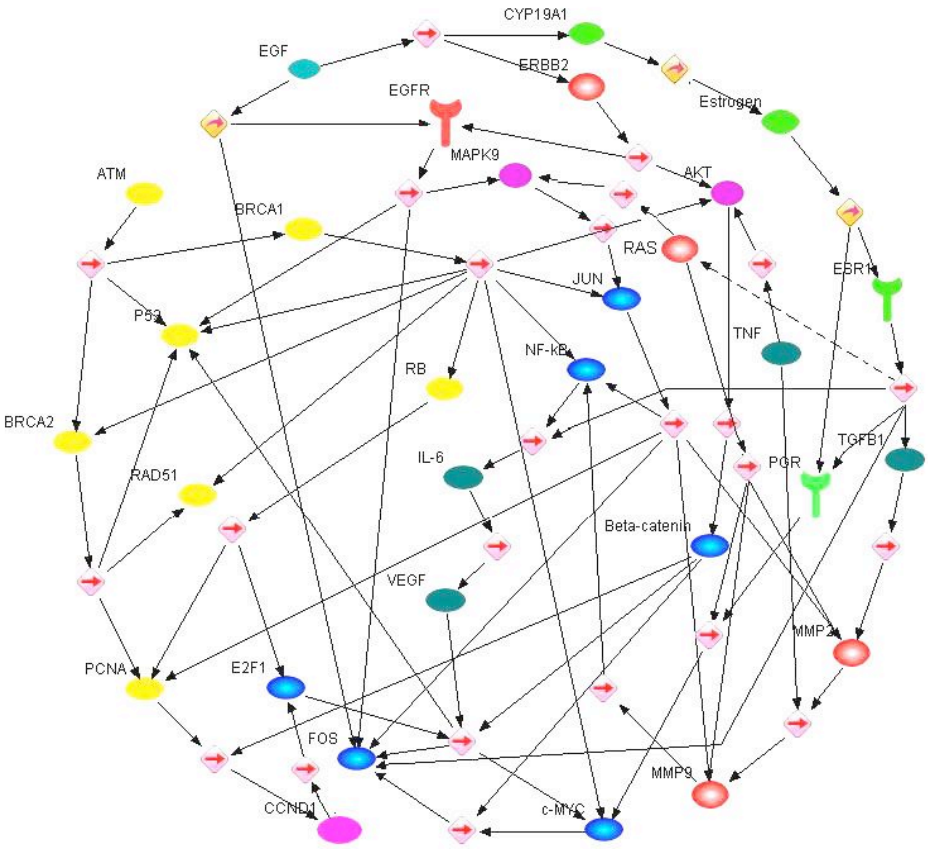

Figure 1. Critical disease pathways in breast cancer.

Table 4. Upstream regulators and downstream targets analysis of key nodes in breast cancer critical disease pathways.

Key nodes	Up stream regulators	Down stream targets
BRCA1	**ESR1**, FRA2, GABPA, TP53BP1, EGF, **SP1**	CDKN1B, CTLP, **MYC**, ZBRK1, Angioprotein-1, TERT, **VEGF**
BRCA2	USF1, USF2, SLUG	BRCC, RAD53/CHK2, RAD51, BARD1, BRCA1, MLH1, Tubulin, SKP2, PALB2
CDK4	**MYC**	**CCND1**, BRCA1
CTNNB1 (β-catenin)	**AKT, TNF**	**CCND1, FOS, MYC**
CYP19A1	USF1, USF2, **EGF**, **IL6**	**ESR1**, PGR, P53
E2F4	BRCA1	**PCNA**, CDK1, **RB, CDK2**, Cyclin A,
ESR1	FOXO3a, SIRT1, RUNX2/ AML3	AR, P53, **TGF, FOS**, **PGR**, BRCA1, CYP1B1, FIX, MMP2, **IL6**
FOS	**EGF, AP1/JUN, ESR1**, **IFNG,** STAT, IL22, SRC	FRA1, IL2, **IL6, IL8**, ET1, MMP1, FLG, P53
ERBB2/ HER2/neu	GABPA, **MYC**, SPI1, AR, EGF	**PTEN, KRAS, CCND1, ESR1, MMP2, MMP9, MYC**
JUN	**EGF, TGF**, CNK, IKK, SENP1	MSH2, **ESR1**
K-RAS	P53, CTF, **SP1**, HER2	MMP2, MMP9, CCND1
MAPK9	**EGFR**	**JUN**, RARA
MMP2	AP-2 α, P53, KRAS, **HER2, ESR1**	**MMP9, TSP1**
MYC	**AP1/JUN**, AP2, STAT, **EGF, SP1**, MAK, TCF4	**CDC25A**, **CDK4, eIF-4E**, **ERBB2**, TERT
P53	**JUN, FOS, AP1**, NF1, PAX5, PTEN	**PCNA**, MSH2, **K-RAS**, PPM1D
MMP9	SDF1, MMP2, TGF, HER2	TSP1, TSP2, **NF-κB**
NF-κB	**MMP9, PTEN**	PCNA, **FOS, MYC**
PCNA	P53, IKK-α, **NFκB, E2F4**, P53, **ESR1, AP1**	**POL-D and- E**, DNA Ligase-1, **RFCs**, MSH3, GTBP, RARA
PGR	**ESR1,** ADA3	CSF, IGFBP
PTEN	P53, **HER2**	**NF-κB**
RAD51		BRCC, ATM, BRCA2, GTBP, P53, BRCA1
VEGF	**SP1, ERK, TGF**, SMAD, **AP1**, BRCA1	**VEGF**-A, VEGF-165, VEGF-145
TNF		**MYC, MMP2, MMP9**

PCNA which is either upregulated or mutated in breast cancer have been found to be regulated by P53, IKK-α, NFκB, E2F4, P53, ESR1, and AP1/JUN from its upstream and PCNA regulates its downstream targets mainly replication machinery key molecules such as POL-D and-E, DNA Ligase, and RCFs etc. All key nodes and their upstream and down stream targets can be considered as drug targets depending on the molecular profile of the specific case of the cancer.

C. Let-7 targets ER and mitogenic signaling pathways and also blocks cell cycle

Next we tried to identify miRs those can potentially target key nodes and their upstream regulators and downstream targets of the critical pathway network. miRs were identified from miR prediction databases (mirBase, PicTar, TargetScan, and miRanda), experimentally identified target database (TarBase), and form extensive Pubmed literature search. Several miRs have been found to target multiple key nodes along with their upstream regulators and down stream targets (**Table 3**) (predicted data not shown). Out of 150 identified targets including key nodes of the critical disease pathways (**Table 4**), a total of 73.3% key molecules are found to be targeted by let-7, miR-125, miR-205, and miR-296 (**Tables 3 and 5**) where they respectively covers 63%, 21.8%, 20.9% and 6.4% key targets. Experimental data show that let-7 targets oncogenes such as RAS and MYC and also inhibits cell cycle machinery by targeting several cell cycle regulators mainly CDC25A, CDK4, CDK6, E2F5-6, HMG2, several cyclins, check point regulators, and DNA polymerases (Johnson et al, 2005; Johnson et al, 2007) (**Table 3**). Predicted targets for let-7 show that it can also inhibit CCND1-2, CYP19A1, ESR2, FGF11, FGFR, IGF1 and IGFR1, IL6 and other ILs, MAPKKs, MMP8, DNA polymerases, and TGFBR (**Table 5**). Interestingly, the data also suggest that let-7 might play a role in targeting DNA damage response and repair genes such as BRCA1, BRCA2, MLH3, and RAD51C (**Tables 3 and 5**). Using miR and a precictions for common miRs for several targets, additional let-7 targets have been identified as ESR1, MMP2, MAPK4-6, RB1, TP53, and GRB2 (**Table 6**).

Table 5. Predicted targets form Target Scan, Pic Tar, and Mir Base.

Target Gene	Gene Name	Target Scan	Pic Tar	Mir Base
AKT3	v-akt murine thymoma viral oncogene homolog 3	miR-125a		
BCL2	B-cell CLL/lymphoma 2	miR-205		
BCL6	B-cell lymphoma 6 protein	miR-205	miR-205	
BRCA1	Breast cancer 1, early onset		miR-205	
CCND1	Cyclin D1	let-7b	let-7a	
CCND2	Cyclin D2	let-7f	let-7a	
CDC25A	Cell division cycle 25 homolog A	let-7d	let-7a	
CDC34	Cell division cycle 34	let-7	let-7a	
CDK11	Cyclin-dependent kinase 11		miR-125a, miR-205	
CDK4	Cell division protein kinase 4			miR-205
COL4A2	Collagen, type IV, alpha 2	let-7	let-7a	
CSF1	Macrophage colony-stimulating factor 1			miR-125b
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1	let-7f	let-7a	
DLC1	Deleted in liver cancer 1		let-7a	
E2F1	E2F transcription factor 1	miR-205	miR-205	miR-205
E2F3	E2F transcription factor 3	miR-125a	miR-125a	
E2F5	E2F transcription factor 5		let-7a miR-205	miR-205
E2F6	E2F transcription factor 6	let-7c	let-7a	
EIF4A3	Eukaryotic translation initiation factor 4A isoform 3			miR-205
EIF4E1B	Eukaryotic translation initiation factor 4E-1B			miR-205
ERBB2	Receptor tyrosine-protein kinase erbB-2			miR-125b
ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3	miR-205		miR-205
ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4	miR-125a miR-205		
ESR2	Estrogen receptor beta			let-7a
ESRRA	Estrogen-related receptor alpha		miR-125a	
FGF11	Fibroblast growth factor 11	miR-98	let-7a	
FGF4	Fibroblast growth factor 4 precursor			miR-205
FGF5	Fibroblast growth factor 5		miR-125a	
FGFR2	Fibroblast growth factor receptor 2	miR-125a	miR-125a	
FGFR4	Fibroblast growth factor receptor 4			let-7a-b
HGF	Hepatocyte growth factor			let-7b
HRAS	GTPase HRas precursor			miR-205
IGF1	Insulin-like growth factor IA precursor			let-7b
IGF1R	Insulin-like growth factor 1 receptor	let-7b		
IGF2	Insulin-like growth factor II precursor			miR-125b
IL10	Interleukin 10		let-7a	
IL13	Interleukin 13		let-7a	let-7a-b
IL16	Interleukin 16		miR-125a	miR-125b
IL2	Interleukin 2			let-7a-b
IL5	Interleukin-5 precursor			miR-205
IL6	Interleukin 6 (interferon, beta 2)	let-7d		
IL6ST	Interleukin-6 receptor subunit beta precursor			let-7b
IL8	Interleukin 8		let-7a	
MAP2K2	Mitogen-activated protein kinase kinase 2			let-7b
MAP2K7	Mitogen-activated protein kinase kinase 7		miR-125a	
MAP3K10	Mitogen-activated protein kinase kinase kinase 10	miR-125a	miR-125a	
MAP3K3	Mitogen-activated protein kinase kinase kinase 3		let-7a	
MAP4K3	Mitogen-activated protein kinase kinase kinase kinase 3	miR-98		let-7a-b
MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4	let-7a	let-7a	
MAPK14	Mitogen-activated protein kinase 14		miR-125a	
MAPK3	Mitogen-activated protein kinase 3			miR-125b
MAPK6	Mitogen-activated protein kinase 6	let-7b		
MAPK9	Mitogen-activated protein kinase 9	mir-205	miR-205	
MLH3	DNA mismatch repair protein Mlh3			let-7a-b
MMP11	Matrix metalloproteinase 11		miR-125a	miR-125b
MMP26	Matrix metalloproteinase-26			miR-205
MMP8	Matrix metalloproteinase-8			let-7b
MSH2	DNA mismatch repair protein Msh2			miR-205
MYC	v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	let-7i		let-7a-b
NFIB	Nuclear factor I/B	miR-125a, miR-205		
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog	let-7f		

POLA2	DNA polymerase subunit alpha B			let-7a
POLI	DNA polymerase iota			let-7a-b
POLL	DNA polymerase lambda			let-7a-b
POLQ	DNA polymerase theta			let-7b
POLR2D	DNA-directed RNA polymerase II 16 kDa			let-7a-b
POLR2G	DNA directed RNA polymerase II polypeptide G			let-7b
POLR3D	Polymerase (RNA) III (DNA directed) polypeptide D, 44kDa	let-7d		
POLR3G	DNA-directed RNA polymerase III subunit G			let-7a
RAD51C	DNA repair protein RAD51 homolog 3			let-7a
S100A1	Protein S100-A1			miR-205
SP1	Sp1 transcription factor		miR-125a	
SP4	Sp4 transcription factor	miR-205		
TGFBR1	Transforming growth factor, beta receptor I	let-7g, miR-125b	let-7a	
TGFBRAP1	TGF beta receptor associated protein -1			miR-205
TNF	Tumor necrosis factor precursor			miR-125b
VEGFA	Vascular endothelial growth factor A	miR-205		miR-205
VEGFB	Vascular endothelial growth factor B			miR-125b

Thus in respect to our breast cancer critical disease pathway, let-7 might potentially inhibit both the estrogen receptor and mitogenic signaling pathways by directly targeting CYP19A1, ESR1, TGFB, RAS, SKP2, MMP2, ILs, and MYC (**Table 7**). In addition to these two pathways, the current evidences suggest that let-7 also can induce cell cycle arrest and growth inhibition by directly targeting several cell cycle regulators (Johnson et al, 2007). It is also found that let-7 can inhibit ITGB3 and angiogenin thus inhibits angiogenesis, cell migration, and metastasis.

D. miR-125 blocks growth factor signaling and cell cycle

The potential second miR for precisely targeting growth receptor signaling was identified as miR-125 which can block the pathway by targeting numbers of key molecules, growth factors, and cell cycle regulators. Identified targets of miR-125 are AKT, ERBB2-4, FGF, FGFR, IGF, MAPKs, MMP11, NFIB, SP1, TGFBR1, TNF, VEGF, CDK11, E2F3, ESRRA (**Tables 3 and 5**). miRanda precictions give additional targets for miR-125 as CTNNB1/ β-catenin, FOS, CDC25A, and IL6R (**Table 6**). Thus miR-125 can potentially inhibit ERBB2 signaling by inhibiting key nodes (ERBB2, AKT, β-catenin, growth factor signaling molecules) along with key transcription factors (FOS, NFIB, E2F3) and cell cycle regulators (CDC25A and CDK11) (**Table 7**).

E. miR-205 and miR-296 targets multiple key nodes of the BC critical disease pathway

From prediction databases it has been found that miR-296 might inhibit multiple key components of all three critical pathways. Identified potential targets of miR-296 are ERBB2, ESR1, MMP2, JUN, CCND1, CCND3, and TGFB1 (**Table 6**). Similarly, miR-205 have been found to potentially target BCL2, BRCA1, CDK11, CDK4, E2F1, E2F5, EIF4A3, EIF4E1B, ERBB3, ERBB4, FGF4, HRAS, IL5, MAPK9, NFIB, S100A1, SP4 and VEGFA (**Table 5**), MMP2, KRAS, E2F6 and FGF1 (miRanda precictions). miRanda common target preciction also shows that EGFR signaling can potentially be disrupted by miR-27, miR-34, and miR-214 (**Table 6**).

IV. Discussion

Population based studies show that the genetic makeup of BC pathogenesis varies from person to person and also varies depending on particular group of population, race, and socioeconomic factors (Gloeckler et al, 2003; Chlebowski et al, 2005; Fejerman and Ziv, 2008). Apart from several genetic alterations, a considerable numbers of miRs have been found deregulated in breast cancer (Iorio et al, 2005; Hossain et al, 2006; Sempere et al, 2007; Si et al, 2007; Yu et al, 2007; Huang et al, 2008; Lehmann et al, 2008).

Table 6. miRanda precictions for common miR targets.

miRs	Targets
let-7	THBS1, CDC25A, POLD3, MMP2, IGF1, E2F5/6, MAPK6, ESR1, CYP19A1, MYC, CCND3, MUC4, MAPK4, STAT2, TP53, RB1, GRB2
miR-27	JUN, EGFR
miR-34	MYC, EGFR, KRAS
miR-125	CTNNB1, VEGF, FOS, CDC25A, TNF, IL6R, E2F2, MMP11, BCL2
miR-205	MMP2, KRAS, E2F6, FGF1,
miR-214	CTNNB1, NFKB1, EGFR
miR-296	ERBB2; ESR1, MMP2, JUN, CCND1, CCND3, TGFB1, NOTCH3

Several recent studies have shown that miRs are promising agents for cancer therapy. miR-17-92 cluster which is involved in lung development (Ventura et al, 2008) is highly upregulated and induces MYC in aggressive small-cell lung cancer (Hayashita et al, 2005). Induced inhibition of miR-17-5p and miR-20a induces apoptosis in lung cancer cells overexpressing miR-17-92 cluster (Matsubara et al, 2007). miR-128b LOH is frequent in NSCLC and restoration of miR-128b is reported to inhibit tumor growth by inhibiting EGFR (Weiss et al, 2008). Similarly, let-7 is downregulated in lung cancer and overexpression or restoration of let-7 represses lung cancer growth (Takamizawa et al, 2004; Fabbri et al, 2007; Inamura et al, 2007; Esquela-Kerscher et al, 2008, Kumar et al, 2008) by inhibiting RAS and MYC (Johnson et al, 2007). In colorectal cancer miR-143 and miR-145 are downregulated (Michael et al, 2003) and overexpression miRNA 143 and miR145 inhibit colon cancer growth by suppressing respectively ERK5 (Akao et al, 2006) and IRS1 (Shi et al, 2007). let-7 which is also downregulated in colorectal cancer induces growth inhibition by lowering RAS and c-MYC expression when overexpressed (Akao et al, 2006). Reconstitution of miR-342 reported to induce apoptosis in colorectal cancer (Grady et al, 2008). Similarly, miR-126 and miR-335 those are lost in primary breast cancers, reduces tumour growth, proliferation, and metastasis when overexpressed (Tavazoie et al, 2008). Inhibition of oncomir miR-21 is reported to suppress MCF-7 cell growth (Si et al, 2007; Cissell et al, 2008). Several other studies show that inhibition of miR-21 inhibits growth of glioblastoma (Chan et al; 2005; Corsten et al, 2007) and hepatocellular carcinoma (Meng et al, 2007). Treatment with miR-7 reduces invasiveness of glioblastoma by suppression EGFR and AKT (Kefas et al, 2008). miR-221 and 222 are also reported to be ideal therapeutic agent for glioblastoma (Medina et al, 2008). miR-203 is lost in CML and ALL and that the epigenetic silencing of miR-203 enhances ABL1 and BCR-ABL1 oncogene expression (Bueno et al, 2008). Restoration of miR-203 expression has been reported to reduce ABL1 and BCR-ABL1 levels and inhibit cell proliferation in CML (Faber et al, 2008). Restoration of several other deregulated miRs in different cancers **(Tables 1 and 2)** and their targets **(Tables 3, 5, 6 and 7)** may also prove beneficial for cancer therapy.

In our current study we demonstrated that, growth factor receptor (EGFR) signaling, estrogen receptor signaling, and DNA repair pathways interplay in breast cancer. EGF, CYP19A1, ESR1, ERBB2, JUN, MMP2, PCNA, AKT, VEGF, NF-κB, Cyclin-D, and CDK4 are found to be key nodes of the entire network those are potentially be good drug targets. The downstream key effecter molecules those are also needed to be targeted are identified as components of replication machinery, DNA polymerases, cell cycle regulators, and transcription factors such as FOS and MYC. let-7 is downregulated in breast cancer and induction of let-7 suppress cancer growth by inhibiting H-RAS and HMGA2 expression (Sempere et al, 2007; Yu et al, 2007). In our study we have found that let-7completely inhibit ER signaling and partially represses growth factor signaling pathway by targeting key components of these pathways. let-7 also have been found to bring cell cycle arrest and inhibition of angiogenesis by targeting several cell cycle and angiogenic regulators and transcription factors.

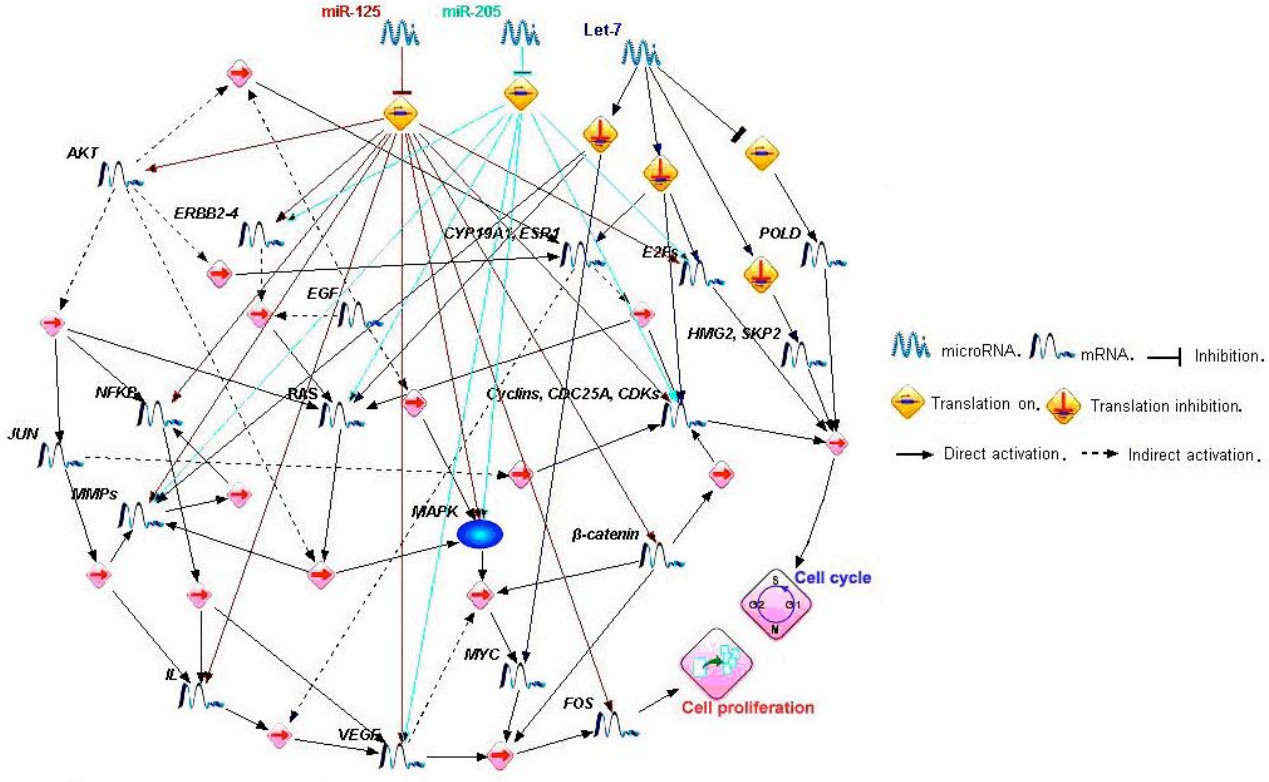

Figure 2. Targets of ler-7, miR-125, and miR-205 in breast cancer critical disease pathway.

Table 7. Key targets covered by four microRNAs of the breast cancer critical disease pathways derived from all analysis.

microRNAs	Targets
let-7	RAS, MYC, CDC25A, CDK4, CDK6, E2F5-6, HMG2, DNA-Polymerases, CCND1-2, CYP19A1, ESR1, ESR2, FGF11, FGFR, IGF1 and IGFR1, IL6 and other ILs, MMP2, MMP8, TGFBR, MAPK4-6, RB1, TP53, GRB2, TGFB, SKP2, ITGB3, and angiogenin
miR-125	AKT, ERBB2-4, FGF, FGFR, IGF, MAPKs, MMP11, NFIB, SP1, TGFBR1, TNF, VEGF, CDK11, E2F3, ESRRA, CTNNB1/ β-catenin, FOS, CDC25A, and IL6R
miR-205	BCL2, CDK11, CDK4, E2F1, E2F5, E2F6, EIF4A3, EIF4E1B, ERBB3, ERBB4, FGF4, HRAS, IL5, MAPK9, NFIB, S100A1, SP4, VEGFA, MMP2, KRAS, and FGF1
miR-296	ERBB2, ESR1, MMP2, JUN, CCND1, CCND3, and TGFB1

Reduced expression of miR-125b correlates with metastasis in breast cancer (Iorio et al, 2005) and the overexpression of either miR-125a or miR-125b inhibit breast cancer growth by inhibiting ERBB2 and ERBB3 at both the transcript and protein level (Scott et al, 2007). Apart from these targets our analysis shows that miR-125 can target multiple key molecules (ERBB2, AKT, β-catenin, FOS, NFIB, E2F3, CDC25A, and CDK11) of the entire network of our breast cancer critical pathways. Similarly, miR-205 is downregulated in breast cancer (Sempere et al, 2007) and we have shown that restoration of miR-205 might inhibit growth factor receptor signaling pathway by repressing ERBB 3-4, FGF, HRAS, MAPK9, NFIB, VEGFA, MMP2, KRAS, CDK4, and E2F1. Another predicted miR i.e., miR-296 have been also found potential to disrupt EGFR signaling by targeting ERBB2, ESR1, MMP2, JUN, CCND1, CCND3, and TGFB1. Thus appropriate combination of these microRNAs can potentially cover all targets **(Figure 2, Table 7)** to inhibit tumor growth and to restore normalcy in breast cancer.

V. Conclusion

In conclusion, our results suggest that let-7 replacement therapy might be effective in estrogen and ERBB2 positive breast cancers. Treatment with either miR-125 or miR-205 or miR-296 has best possibility to be effective in ER negative breast cancers overexpressing ERBB2. A combination of let-7 along with any one of the above mentioned three miRs might be an efficient future molecular medicine irrespective of the type of breast cancer. Being miR a natural agent, miR replacement therapy will not evoke any side effect those are occasionally found in chemotherapy.

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