

MINI-REVIEW

The Research Progress of the Interactions between miRNA and Wnt/beta-catenin Signaling Pathway in Breast Cancer of Human and Mice

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Abstract

MicroRNA expression is a research focus in studies of tumors. This article concentrates attention on potential links between tumors caused by mouse mammary tumor virus (MMTV) and human breast cancer, in order to provide theoretical basis for using mouse model to search for miRNA effects mediated by Wnt/beta-catenin signaling in human breast cancer. By analyzing interactions between miRNAs and the Wnt/beta-catenin signaling pathway in breast cancer, we hope to cast light on more biological functions of miRNAs in the process of tumor formation and growth and to explore their potential value in cancer diagnosis, prognosis and treatment. Our endeavor aimed at providing theoretical basis for finding safer, more effective methods for treatment of human breast cancer at the miRNA molecular level.

Keywords: miRNA - MMTV - breast cancer - Wnt/beta-catenin signaling pathway - mouse and man

Asian Pac J Cancer Prev, **15** (3), 1075-1079

Introduction

In 1993, Lee discovered a gene, *lin-4*, which contains *lin-4* mRNA 3' UTR complementary antisense sequence that affected development in the *C. elegans* (Lee et al., 1993). In 2000, Reinhart found another small RNA-*let-7* in the nematode (Reinhart et al., 2000). Whereafter, Pasquinelli found that the expression pattern of *let-7* in the evolution of more distantly related species were highly conservative, which revealed the universal regulations of *let-7* in gene expression (Pasquinelli et al., 2000). The earliest evidences for miRNAs related to tumors came from the study of Chronic Lymphocytic Leukemia (CLL). For now, researchers have found more than 50 % of miRNA genes in the chromosome fragile site, and these fragile sites in malignant tumors were often lack, amplification and rearrangement, which prompted that unbalanced expression of miRNAs played an important role in tumor pathogenesis (Huang et al., 2008). MiRNAs are complementary to 3' UTR sequence motifs and lead negative post-transcriptional regulation: inhibiting or degrading mRNA expression, which means are used depending on the degree of base complementary pairing of miRNAs with its target molecules mRNA. MiRNAs or mRNAs can realize the one-to-many combination between mRNA or miRNAs, according to the prediction of vertebrate, a miRNA can regulate more than 400 target genes, and form a complicated and precise regulation network (Hutvagner et al., 2002; Lai, 2002; Zeng et al.,

2003). At present, in higher eukaryotic cells, the miRNA genes account for 1 % of the known genes and about 30 % of the genes are regulated by miRNAs.

MMTV belongs to beta retrovirus. It can cause breast tumor in mice. The recent study found that human breast cancer and mouse lymphoma was associated in etiology. Researchers revealed that 56 % of Australia's breast cancer and 76 % of human breast cancer cell lines have similar genetic sequences with MMTV by using PCR to detect specimens (Mok et al., 2008).

Wnt/beta-catenin signaling pathway is a highly conserved way in evolutionary processes. The main members of the signaling pathway including Wnt protein and its receptor, beta-catenin, antigen presenting cells, T-cell factor (TCF), etc. Beta-catenin, the key ingredient, can not only combine with E-cadherin, TCF, lymphatic enhancement factor (LEF), but can also contact with the compound which composed by glycogen synthase kinase 3 β (GSK-3 beta), adenomatous polyposis coli (APC), Axin. By combining with different compositions, the level of beta-catenin in cytoplasm and nucleus will changes, which influences the expression of certain genes. The pathway plays an important role in vital process, such as in embryonic development, cell apoptosis, etc. In normal mature cells Wnt pathways in a closed state, but it shows up an abnormal activation in the progress of tumor. So far, the research of breast cancer in mice has been used to explore the mechanism of human breast cancer, this paper mainly introduces the interaction between Wnt/

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beta-catenin signaling pathway and miRNAs in human breast cancer and breast cancer in mice, which may provide theoretical reference for finding safer, more effective treatments for human breast cancer at the miRNA molecular level.

The potential links between MMTV and human breast cancer

Indik found MMTV could rapidly spread in human breast cancer cell line and ultimately, infect all the cells in the culture medium, which showed that human cell was ideal host of MMTV. In addition, cats infected a virus which had similar gene sequences with MMTV would likely to infecting human as intermediate host. Their research suggested that MMTV cross-species transmission was possible and might be etiology mechanism of human breast cancer (Indik et al., 2005). More than 90 % of breast cancer in mice is associated with MMTV. Furthermore, human breast cancer and breast cancer in mice on the gene phenotypic and molecular transduction pathways are very similar. These evidences directly or indirectly point out that human breast cancer caused by retrovirus which is very close to MMTV, namely human homologue of the mouse mammary tumor virus (HHMMTV). Luo examined 131 samples of Chinese female breast cancer tissue. Positive rate of MMTV-like genetic sequences was 16.8 % in their experiment (Luo et al., 2006). The current reports showed difference positive rate in various areas, North America (36 %), Western Europe (37.7 %), and the incidence of breast cancer in mice were relatively consistent with the incidence of human breast cancer in same area (Zapata et al., 2007), which prompted MMTV had been implicated in human breast cancer.

In addition, Wang discovered a gene sequence with more than 95 % similarity of MMTV env (Wang et al., 1995), While the sequence was compared with other known human retrovirus gene sequence and human virus gene sequence, such as HERV-K10 (Ono et al., 1986; Wang et al.2001), the similarity was less than 18 %. In addition to detecting breast cancer group, researchers also detected a large quantity of normal breast tissue samples, and carried out contrast test on the breast cancer tissue and normal breast tissue in same individual. The detection rate of MMTV similar gene sequence in the normal breast tissue was 0-1.8 %. So, some researchers believed that the MMTV-like gene sequence in breast cancer tissue was exogenous nucleotide (Melana et al., 2001; Theodorou et al., 2007). Above studies show that human breast cancer and MMTV or MMTV-like virus have significant correlation. Hence exploring the relationship between miRNA and Wnt/beta-catenin signaling pathway in breast cancer in mice can lay a foundation for researching human breast cancer in the same field, which plays an important role for finding new therapeutic targets in the miRNA molecular level.

The relationship between Wnt/beta-catenin signaling pathway and breast cancer

It is very similar that human breast cancer and breast

cancer in mice at the gene phenotypic and molecular transduction pathways, so we can use mouse model to study human breast cancer in the molecular level. Existing references report MMTV is able to insert its viral genome in the mouse genome and to promote activation of int, Wnt and FGF etc. oncogene (Liu et al., 2001). The Wnt pathway is regulated by the Wnt-1 gene. Under normal circumstances, Wnt-1 gene expresses in adult male mice testicles and developmental central nervous system in mice, while in the 4T1 and MCF7 cells, breast cancer stem cells express Wnt-1 and beta-catenin signaling molecules at a high level (Patrawala et al., 2005; Kruger et al., 2006). Wnt/beta-catenin signaling pathway plays an important role in tumor formation and normal breast development. Transferring the Wnt/beta-catenin gene into the mammary gland stem cells, the proportion of breast side group cells in mice increased 9 times, while mammary gland development was ceased by blocking beta-catenin signaling in mammary gland acinus progenitor cells, which hinted that the beta-catenin was survival factor of mammary gland stem cell (Tepera et al., 2003). Tsukamoto confirmed mammary gland epithelial hyperplasia result from the high level expression of wnt-1 gene in MMTV-Wnt-1 transgenic mice (Tsukamoto et al., 1988). Some studies also showed that Wnt-1 gene expression in cells could activate Wnt-receptors on the adjacent and its own cell membrane, then subsequent process caused epithelial-mesenchymal transitions (EMT) of mammary gland, and markers in breast cancer stem cell of MMTV-Wnt-1 transgenic mice expressed significantly high (Parkin et al., 1996; Stingl et al., 2006). Abnormal activation of Wnt pathway can interfere with the mammary gland stem cell self-renewal, induce abnormal proliferation of stem cells to form breast cancer stem cells, finally, lead to form breast tumor. Therefore, There are new treatments for breast cancer at molecular level, which mediated by Wnt/beta catenin signaling pathway.

The interaction between Wnt/beta-catenin signaling pathway and miRNAs in breast cancer

The main miRNAs which regulate the Wnt/beta-catenin signaling pathway

Plenty of evidences show that many miRNAs can regulate the Wnt/beta-catenin signaling pathway, such as miR-200 family. Functions of miR-200 family members are maintain E-cadherin expression and the epithelial phenotype (Gregory et al., 2008; Huang et al., 2010). MiR-200a can reduce transcription that mediated by beta catenin. It targets the mRNAs of E-cadherin repressor proteins, ZEB1 and ZEB2, then upgrades the total E-cadherin available for binding to beta-catenin and reduces formation of the cell-cell adhesion compound, Later on, beta-catenin is phosphorylated at Ser33, Ser 37, Thr 41 and Ser45 by the tumor destruction compound and degraded by the ubiquitin/proteasome system (Korpál et al., 2008). In epithelial cells, low expression of miR-200 increases the free monomers of beta-catenin in the cytoplasm and nucleus, leads ZEB1 and ZEB2 to increase and E-cadherin to reduce, and finally, causes

epithelial-mesenchymal transition (Gregory et al., 2008; Burk et al., 2008; Park et al., 2008; Kong et al., 2009; Tryndyak et al., 2010). In vitro, enforcing the expression of miR-200 family in NMuMG murine breast epithelial cells, epithelial-mesenchymal transition which caused by transforming growth factor-beta (TGF- β) is inhibited (Korpál et al., 2008; Kong et al., 2009). In high invasive MDA-MB-231 human breast cancer cell line, restoring the expression of miR-200c can resume normal expression of E-cadherin and largely re-establish epithelial phenotype (Burk et al., 2008; Park et al., 2008; Chen et al., 2011). The regulations on E-cadherin indirectly make the miR-200 family to situate at a high position in the Wnt/beta-catenin signaling pathway, and the effect is remarkable of cascade reaction. Therefore miR-200 family is expected to become a potential target for the treatment of breast cancer. Cai found in the mammary gland cell lines, overexpression of miR-374a could promote EMT and distal metastasis, both in vitro and in vivo. MiR-374a activated the beta-catenin and direct effected on multiple negative regulators including tumor suppressor genes, WIF1, PTEN and WNT5A in Wnt/beta-catenin signaling pathway. MiR-374 utilized the function of Wnt/beta-catenin signaling pathway to accelerate EMT and distal metastasis. The MCF7/miR-374a and the 4T1/miR-374a cells, as well as their corresponding vector control cells, were transplanted into the mammary gland fat pads of nude mice, mice bearing MCF7/miR-374a and 4t1/ miR-374a tumors displayed prominent lung metastasis, while no visible metastasis was found in mice transplanted with control MCF7 cells. Infecting miR-374a inhibitor into MDA-MB-435 cell line, researchers found the migration of beta-catenin in nuclear was reduced, subsequently, the activity of TCF/LEF were decreased too. MiR-374 constitutively activates Wnt/beta-catenin signaling pathway, it may become a target for the treatment of early metastatic breast cancer (Cai et al., 2013).

In addition, miR-21 can suppress Wnt-1 gene expression at the translation level. miR-21 antagonism effect, by transfecting miRNA inhibitors or exogenous adding Wnt-1, inhibits differentiation of monocyte derived dendritic cells (MDDC), whereas MDDC plays an important role in antiviral and antitumor immune response, which shows miR-21 is an important regulator in the process of MDDC differentiation (Hashimi et al., 2009). Before discovering the regulation relationships between miR-21 and Wnt-1 gene, researchers revealed miR-21 could regulate programmed cell death 4 (PDCD4) and the proto-oncogenes Bcl-2. MiR-21 over expression reduced PDCD4 gene expression and up-regulated Bcl-2 gene expression, eventually, led to reduce cell apoptosis and to accelerate tumor growth (Si et al., 2007; Frankel et al., 2008; Asangani et al., 2008; Yan et al., 2008). High expression level of miR-21 in the organization may be a symbol of cancer, including breast cancer, lung cancer, colon cancer, pancreatic cancer, prostate cancer, gastric cancer (Volinia et al., 2006). Zhu found suppressor gene Tropomyosin1 (TPM1) was also a target of miR-21 in the mammary gland cell line, MCF-7, and miR-21 regulated the expression of TPM1 at translation level (Zhu et al., 2007). The above researches show the regulatory

mechanism of miR-21 in breast cancer is very complex, expect for the Wnt/beta catenin signaling pathway, there are other regulation pathways. Asaga used RT-PCR to test 102 samples of I, II, III or IV breast cancer patients according to the stages divided by American Joint Committee on Cancer (AJCC) and 20 healthy women serum samples. They found that the concentration of miR-21 related with AJCC stages, but had nothing to do with estrogen receptors, status and age (Asaga et al., 2011). The above results show that miR-21 plays an important role in diagnosis and prognosis for the early breast cancer. In vitro, Si transfected miR-21 blocker into MCF-7 breast cancer cell line and found breast cancer cell growth was inhibited. MCF-7 transfected blockers or not was injected into breast female nude mice, and researchers discovered blocker effect was better than that on breast cancer cell line (Si et al., 2007). The miRNA inhibitors are expected to become new treatment for abnormal regulation in cancer stem cells which caused by oncogenic miRNAs.

The main miRNAs which regulated by the Wnt/beta-catenin signaling pathway

At present, studies find that Wnt/beta-catenin signaling pathway in cancer stem cells can also regulate mature miRNAs. Among the few Wnt-regulated miRNAs, Let-7 is one of them. Let-7 is a key regulator of breast cancer stem cell self-renewal and differentiation (Yu et al., 2007). Lin28 is one of the regulators of regulating stem cell activity and it is very rich in embryonic stem cells. Lin28/Lin28B function as negative regulators of let-7 can accelerate the renewal of let-7 precursor but they prevent let-7 processing mediated by both DroshaIII and DicerIII, let-7 targets Lin28 and downregulates its expression in turn, which reveal that a regulatory feedback loop exists between let-7 and Lin28 (Heo et al., 2008; Piskounova et al., 2008; Rybak et al., 2008; Newman et al., 2008). Cai experiments confirmed the Wnt/beta-catenin pathway could reduce the quantity of mature let-7 rather than affect its primary transcript, and proved lin28 as a novel direct downstream target of Wnt/beta-catenin pathway. Loss of function of Lin28 weakened breast cancer stem cell expansion and Wnt/beta-catenin pathways mediated let-7 inhibition. Therefore, Wnt/beta-catenin pathway, Lin28, and let-7 connect in one signal cascade. Transfecting a modified lin28 siRNA or a let-7a agomir into the premalignant mammary tissues of MMTV-wnt-1 mice could successful rescue the stem cell phenotype driven by Wnt/beta-catenin pathway. Breast cancer in mice, the Wnt/beta-catenin pathway could cause Lin28 increases and let-7 decreases (Cai et al., 2013). Low expression of let-7, direct targeted on inhibition of protein-serine-threonine kinases Pak1, reduces the abilities of migration and invasion of breast cancer cell (Reddy et al., 2008). Other 2 miRNAs, miR-15 and miR-375 regulated by Wnt/beta-catenin pathway were hinted by Cai experiments, and both of them displayed downregulation in breast cancer stem cells. Wnt/beta-catenin pathway regulated miR-15 maturation, rather than its transcription. However, the underlying mechanism is unknown (Martello et al., 2007). For miR-375, its function and how regulated by the Wnt/beta-catenin pathway are also unknown

(Ladeiro et al., 2008). In addition, the Wnt/beta-catenin pathway could also affect the production of primary miRNA (pri-miRNA). Extracellular signal molecules, WNT3a, activated Wnt signaling pathway, afterwards, the complexes of beta catenin, TCF4 and LEF1 moved into cell nucleus and combined with a common conservative sequence, A-C/G-A/T-T-C-A-A-A-G motifs, in promoter of target genes (Hatzis et al., 2008) finally, regulated the c-myc, cyclin D, c-Jun and AKT1 etc. gene expression. While certain miRNAs share common promoter with most genes, thus Wnt/beta-catenin also can regulate the expression of some miRNAs. There are many components in Wnt/beta-catenin pathway, different affections of components on certain miRNAs can change the expression of the miRNAs, so the regulation network, is likely to be a new breakthrough for cancer treatment.

Conclusions

Mechanism of breast cancer occurrence and development is complex. At present, experts can't cure breast cancer thoroughly. Through analyzing the potential relation between human breast cancer and breast cancer in mice, and utilizing the characteristic expression of Wnt-1 gene in breast tumor, which helps to explore the interactions between miRNAs and Wnt/beta-catenin signaling pathway in breast cancer. So mice and mammary gland cell line are good materials for the basic research on human breast cancer to find the interaction networks of miRNAs and Wnt/beta-catenin signaling pathway, to speculate the influences of miRNAs in formation, development and treatment of human mammary gland carcinoma, and ultimately, to find out new targets for the treatment of human breast cancer at miRNAs molecules level mediated by Wnt/beta-catenin signaling pathway.

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