Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Opinion
Volume 11 Issue 5 - August 2018
DOI: 10.19080/CTOIJ.2018.11.555822

Canc Therapy & Oncol Int J

An Innovative Therapeutic Approach for Breast Cancer: Engineered Mesenchymal Stem Cell-Derived Exosomes By Mir-145

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Submission: August 11, 2018; **Published:** August 28, 2018

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Opinion

Genetic changes cause progression and cancer metastasis, so the recognition of these changes will not only increase our understanding of the underlying mechanisms of cancer but also promote specific treatments in this area. Breast cancer has importance due to the progressive accumulation of multiple gene mutations that are associated with epigenetic disorders [1,2].

Breast cancer is defined as an out of control change in cells growth of breast tissue, which is caused by abnormal growth in the milk glands (lobules) or in the ducts that connect the lobules to the nipple (duct) [3]. Breast cancer is the most common cancer in women and the second leading cause of death[4].Every year about one million women are diagnosed with this cancer worldwide. In the United States near to 255180 new cases are detected and the estimated mortality rate has been reported about 40,610 cases in 2017 [5].

Recent studies have shown that microRNAs (miRNAs) are a group of non-coding small RNAs regulating gene expression at the level of RNA by binding to the 3'UTR region of gene and prevention of its expression. These have vital roles in differentiation, proliferation, angiogenesis, and metabolism, so a disruption in these processes is expected to have consequences for cancer formation [6-9].

Several miRNAs have been introduced and studied with antitumor properties in breast cancer. MiR-145 is among the most important of them. MiR-145 is located on chromosome 5, which is a fragile region in the genome. This miRNA was first detected in mice and, after a short time, was also detected in human [10]. miR-145 had been identified as a tumour suppressor miRNA in various types of cancers such as kidney, prostate, bladder, lungs, and intestines. It can be delivered to target tissues and remains functional long enough to knock down the expression of the target protein [11]. However, the performance of miR-145 had not been investigated in breast cancer until 2016 when a study found that miR-145 was significantly reduced in breast cancer cell lines and tissues [12].

Further studies have shown that the ectopic expression of miR-145 reduces the proliferation and mobility of breast cancer cells, and its inhibition can amplify cell proliferation, migration, and invasion in vitro. These findings indicate that miR-145 acts as a tumour suppressor and that reduction of its expression could be involved in the development and metastasis of breast cancer[13]. Several genes in various cancers have been identified as target for miR-145 such as Matrix metalloproteinases (MMPs) [13], Insulin receptor substrate 1 (IRS1) [14], Homeobox A9 (HOXA9) [15], SRY-box 9 (SOX9) andAdducin 3[16], Disintegrin and Metalloproteinase domain-containing protein 17 (ADAM17) [17], Octamer-binding transcription factor 4 (OCT4) [18], Kruppel-like factor 4 (KLF4) [19], p70S6K1 [20], c-myc[21], mucin1 [22], and Rho-associated protein kinase 1 (ROCK1) [13].

In one study, it was shown that this function results from the targeting of the ROCK1 protein by miR-145. ROCK1 adjusts cell migration and connects to its substrate and controls rearrangement of the actin cytoskeleton. Increased expression of ROCK1 is associated with inhibition of this protein, which is associated with decreased mobility and cell invasion [13].

Also, Ding et al. showed that miR-145 can either directly or indirectly cause inhibition of breast cancer cells to proliferate or migrate through regulating TGF-β1 expression [23].So that, miR-145 can be recognized as a target for treatment and diagnosis of breast cancer. To do so and for creating any therapeutic effect by miR-145, targeted delivery of miRNA into tumour cells should be achieved.

According to evidences, mesenchymal Stem Cells (MSCs) are considered as appropriate tools to deliver cancer therapeutic agents. Although these cells are commonly present in bone

marrow, they can be isolated from various sources such as adipose tissue, liver, spleen, thymus, umbilical cord blood, placenta, Wharton's jelly, brain, lung, dental pulp, salivary glands, peripheral blood and some other tissues [24-26]. They are capable secretory cells which release a large number of extracellular vesicles (EVs) in the size range of 40-120 nm, called exosomes [27]. Exosomes are small vesicles with a phospholipid bilayer membrane and endocytic origin. In recent years a special attention has been paid to their relation with biologic and pathophysiologic processes. There is a growing body of evidences indicating that interaction between stem cells and human tumour cells in exchanging biological information is done via exosomes. These EVs are naturally enriched with miRNA and can transfer their content to recipient cells. They are able to exert phenotypic effect by playing role in processes like tumour genesis, angiogenesis, and tumour metastasis [28].

Previously, MSCs-derived exosomes were engineered with anti-mir-9 through transient transfection of parent cell [29]. Furthermore, in an in vivo model of glioma, some promising therapeutic effects were observed after direct injection of MSCs-derived exosomes, supplemented with mir-146, into the tumour[30].

Studies have confirmed the potential of applying exosomes as efficient vehicles for the delivery of miRNA to targeted cells and verified the inhibitory ability of miR-145 against various cancer types, especially breast cancer.Consequently, it could be strongly recommended that delivery of miR-145 via MSCs-derived exosomes may consider as an innovative approach against breast cancer.

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How to cite this article: HodaFazaeli, Ali Kowsari, Mohsen Sheykhhasan. An Innovative Therapeutic Approach for Breast Cancer: Engineered Mesenchymal Stem Cell-Derived Exosomes By Mir-145. Canc Therapy & Oncol Int J. 2018; 11(5): 555822. DOI: 10.19080/CTOIJ.2018.11.555822

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