Regulation of Nuclear Excision Repair (NER) by MicroRNA for treatment of breast cancer

Breast cancer is one of the most common cancers for women in the US, and it is second only to lung cancer in cancer related deaths in women. At the current rate of incidence, annually over 268,000 new cases of breast cancer are estimated to be diagnosed and it is expected to result in deaths of over 41,000 women. Although there are multiple therapies currently available for breast cancer, resistance of malignant cells to chemotherapeutic agents is one of the major challenges for clinical efficacy. Many cancer chemotherapy agents, such as cisplatin and doxorubicin, act by targeting the DNA of cancer cells, which result in genomic damage and hence lead to apoptosis of cancer cells. However, a highly active DNA repair pathway in cancer cells often reverse the effect of these therapies by removing the drug-induced DNA damages, resulting in drug resistance and tumor recurrence. One of the major DNA repair mechanisms associated with resistance to genotoxic therapies is the Nucleotide Excision Repair (NER) pathway. Late stage breast malignancies demonstrate a significant increase in NER comparative to healthy breast tissue or Stage I breast cancer. Therefore, NER is considered a significant reason for clinical resistance to genotoxic anticancer agents in late stage breast cancer. In this context, it is evident that combining NER regulating or suppressing agent with currently used genotoxic chemotherapy drugs will be more effective in treating late stage breast cancer. Considering this unmet therapeutic need, researchers at NSU implemented novel methods to suppress or inhibit the NER mechanism by inhibiting expression of genes crucial for this process. This therapeutic process involves use of microRNA compositions for regulating or suppressing functional capacity of NER in breast cancer cells by targeting three genes essential for NER pathway.

Technology

The proposed technology invented by Dr. Jean Latimer involves a method for regulating NER function in malignant cells for the treatment of breast cancer using the identified microRNA. Scientific findings reported by the inventor has shown that NER dysregulation is associated with breast cancer and gain of NER function is linked with cancer progression. This enhanced NER activated is implicated as a cause of increased aggressiveness and chemotherapy resistance observed in late stage breast cancers. The technology described here utilizes administration of a specific microRNA for suppressing NER in malignant cells, thus making them more vulnerable to chemotherapeutic agents. To identify the ideal microRNA, researchers at NSU evaluated 800 microRNAs for their possible involvement in NER function. Through these efforts, the identification and application of a specific microRNA was demonstrated to be effective against three different late stage breast cancer cell lines. The targeted therapeutic application of this microRNA can be aimed at inhibiting or suppressing genes that are essential for NER function in malignant cells. This invention offers a method of NER regulation in breast cancer, and potentially might be used as the

platform for developing new therapeutic procedures that can have increased clinical efficacy for treating late stage breast tumors with highly proficient NER function and resistance to existing genotoxic chemotherapy regimens.

Application

- For treating late stage breast cancer and overcoming drug resistance in breast cancer
- This technology can be used to enhance sensitivity of malignant cells to chemotherapeutic agents/drugs that target DNA
- The identified microRNA can be administered either by itself or in conjunction with established genotoxic chemotherapy agents for breast cancer to achieve enhanced clinical efficacy

Advantages/Benefits

- Application of the identified microRNA concurrently with genotoxic chemotherapeutic drugs will offer increased clinical efficiency and better patient outcome
- Suppressing/inhibiting NER will enable therapies to overcome drug resistance in some forms of late stage breast cancer and thus reduce likelihood of tumor recurrence
- Identified microRNA strands are designed to specifically target three genes that are essential for the NER pathway
- Scientific studies have shown that this microRNA is abundantly expressed in non-malignant/healthy breast tissue as well as in heart and liver. Therefore, intravenous administration of this biologic is less likely to have harmful non-specific effects on healthy tissues

Status of Development

- Impact of the identified microRNA on NER pathway and cell proliferation was evaluated in three cell lines for late stage breast cancer (MDA-MB-231, MCF-7 and JL BTL-12)
- Both strands of the microRNA, the guide strand and passenger strands, successfully suppressed gene and protein expression for all the three target genes
- NER was significantly suppressed by both strands of the identified microRNA in three breast cancer cell lines that are known to be highly NER-proficient

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Information on Inventors

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