MicroRNA Treatment for Breast and Ovarian Cancer

Published date: May 14, 2019

Technology description

Turns the Cancer Cells' Own Genetics Against Them to Accelerate Cell Death with Potentially Lower Risk of Side Effects for Patients

This therapeutic microRNA is selectively cytotoxic to breast and ovarian cancer cells that harbor mutations in the DNA repair components BRCA1 or 2. Twenty percent of ovarian cancer patients and ten percent of breast cancer patients carry the BRCA1 or 2 mutations. Due to defects in the homologous recombination DNA repair pathway, such cancers become dependent on other DNA repair pathways for survival and proliferation, such as the pathways mediated by PARP1 and CtIP. There are now three FDA-approved PARP1 inhibitors for therapy of breast or ovarian cancers with BRCA1 or 2 mutations, olaparib, niraparib, and rucaparib. These drugs can be limited by their side effects and by the development of resistance by the cancer.

Researchers at the University of Florida have discovered that transducing a microRNA, mir223-3p, into BRCA1 or 2 mutant cancers results in cell death at lower concentrations than olaparib. In addition, mir223-3p is cytotoxic even to BRCA1-mutant breast cancer cells that have developed resistance to olaparib. While mir223-3p is expressed in most normal cells and many cancers, BRCA1 and 2 mutant cancer cells have repressed it, because they cannot proliferate in its presence. Since it is expressed in most normal cells, there would be little normal tissue toxicity when using it as a treatment for cancers that have repressed it.

Technology

Cancers with defects in homologous recombination DNA repair such as the BRCA1 or 2 mutated cancers cannot tolerate any downregulation of back-up DNA repair components, such as PARP1 and CtIP. Mir223-3p normally regulates the expression of these repair components. BRCA1 or 2 mutant cancers repress expression of mir223-3p to maintain high levels of expression of these back-up DNA repair components. To counter this, researchers restore the expression of this microRNA in cancer cells with homologous recombination repair defects. This results in the death of cancer cells from replication fork collapse due to lack of any DNA repair pathway that can resolve replication stress. Using mir223-3p to repress production of PARP1 and CtIP promotes cancer cell death at higher rates than olaparib. By transducing mir223-3p into these cancer cells, researchers are able to prevent PARP1 and

CtIP from being translated into functional proteins. In addition, because mir223-3p employs a mechanism different from olaparib to inhibit PARP1, the two therapies could be used together to prevent the development of resistance. Alternatively, mir223-3p can be used when BRCa1 or 2 cancers become resistant to the FDA-approved PARP1 inhibitors.

Application area

Treatment for breast and ovarian cancers derived from the BRCA1 or 2 mutations that rely on DNA repair pathways. This therapy can also be used in other cancers with defects in homologous recombination such as the BAP-1 mutant mesotheliomas, uveal melanomas, cholangiocarcinomas or renal cell carcinomas.

Advantages

Could be used when BRCA1 or 2 mutant cancers become resistant to the FDA-approved PARP1 inhibitors
Is cytotoxic to BRCA1 or 2 mutant cancers by repressing translation of multiple DNA repair components that these cancer cells are addicted to
Is cytotoxic to BAP1 mutant cancers such as mesothelioma
Is not toxic to normal cells, lowering risk of side effects

Institution

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