Exploiting the role of miR-155 in triple negative breast cancer via CRISPR/Cas9 based genome editing

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Breast cancer is a global health concern, with around 2.3 million diagnosed cases annually. Triple negative breast cancer (TNBC) is a heterogeneous disease, constituting 10-20% of all new breast tumors and lacking the biomarkers that can be effectively targeted in the clinical practice (estrogen receptor (ER), progesterone receptor (PR), and HER2). Most TNBC exhibits aggressive behavior and poor prognosis due to high rates of distant metastases, leading to elevated mortality rates. Despite the efforts to explore alternative strategies, the absence of effective targeted therapies makes TNBC treatment a remaining challenging task for clinicians.

The discovery that dysregulation of microRNAs (miRNAs) and epigenetic factors play a role in carcinogenesis and cancer progression has led to the suggestion that miRNAs could be a potential target for cancer treatment. Among the various miRNAs linked to cancer, miR-155 is one of the most frequently overexpressed miRNAs in solid tumors, as well as in hematological malignancies, including breast cancer. Herein, we elucidated the role of miR-155 in TNBC by demonstrating its upregulation in various TNBC cell lines. A clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 genome editing system targeting miR-155 was designed and validated. Disruption of miR-155 expression in TNBC cells impaired cell proliferation, induced a G2/M cell cycle arrest, inhibited cell migration, and triggered the intrinsic apoptosis signal pathway through the downregulation of anti-apoptotic Bcl-2 and Bcl-XL proteins, and upregulation of pro-apoptotic Bax protein and apoptotic protease Caspase-3. Moreover, extracellular vesicles (EVs) derived from epithelial cells demonstrated the ability to encapsulate and deliver CRISPR/Cas9 DNA plasmid into TNBC cell lines. Altogether, these findings provide a proof-of-principle for a targeted, precise, and effective delivery approach for in vitro CRISPR genome editing in TNBC tumors.