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MAINTENANCE OF CANCER STEM CELLS BY miRNA

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Cancer stem cells (CSCs) are considered to play a central role in the cancer progression, metastasis and the development of drug resistance. MicroRNAs (miRNAs) have important roles in regulating CSC properties and are considered to be potential therapeutic targets. Diverse aberrantly expressed miRNAs have been reported in ovarian cancer cells. However, there have been few reports about miRNAs that were associated with stemness and progression of ovarian cancer. In this study, miRNA nano string profiling analysis was performed to screen crucial miRNAs associated with characteristics and maintenance of CSCs in ovarian cancer. We found that miR-328-3p was remarkably upregulated in ovarian CSCs isolated from both ovarian cancer cell lines and primary ovarian tumors compared to their corresponding bulk cancer cells. We further demonstrated that enforced expression of miR-328-3p in ovarian cancer cell lines expanded the population of ALDH+ cells, enhanced their sphere formation ability, as well as increased their tumorigenicity. While inhibition of miR-328-3p limited the ALDH+ cell population, reduced their sphere formation capacity, and decreased their tumorigenicity. The orthotopic ovarian xenograft assay also demonstrated that inhibition of miR-328-3p impedes tumor growth and metastasis. The mechanistic investigation revealed that repressed ERK1/2 phosphorylation in ovarian CSCs, mainly due to reduced level of reactive oxygen species (ROS), contributes to the enhanced expression of miR-328-3p, and the maintenance of CSCs. Finally, we identified DDB2 as a direct target of miR-328-3p. Given our previous finding that DDB2 is capable of limiting the CSC population in ovarian cancers, we conclude that highly expressed miR-328-3p in ovarian CSCs, probably due to repressed ERK1/2 activity, inhibits DDB2 expression, resulting in the expansion of these CSCs. Thus, targeting miR-328 could be exploited to a novel strategy to eradicate CSCs in ovarian cancer.

BIOGRAPHY

Qi-En Wang is an Associatet Professor in the Department of Radiology and Comprehensive Cancer Center at the Ohio State University. Dr. Wang received his Bachelor Degree in Preventive Medicine in Shanxi Medical College in 1992, and obtained his PhD from Beijing Medical University in 1997 in China. Then, Dr. Wang worked as a Lecturer and Associate Professor at Peking University Medical Center for 4 years. During this time, his research was focused on understanding how gene and environmental exposure interact in carcinogenesis. In 2001, He joined Dr. Altaf Wani's laboratory at the Ohio State University in the United States of America to study the mechanism of DNA repair as a Research Associate and Research Scientist. Since 2011, He has become a Tenure-track Assistant Professor at the Ohio State University, and was promoted to Associate Professor with Tenure in 2017.

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