論 文 要 旨

（ *microRNA-99a-5p* induces cellular senescence in gemcitabine-resistant bladder cancer by targeting *SMARCD1* ）

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Patients with advanced bladder cancer are generally treated with a combination of chemotherapeutics, including gemcitabine, but the effect is limited due to acquisition of drug resistance. Thus, in this study, we investigated the mechanism of gemcitabine resistance. First, gemcitabine-resistant cells were established, and resistance confirmed *in vitro* and *in vivo*. Small RNA sequencing analyses were performed to search for miRNAs involved in gemcitabine resistance. *miR-99a-5p*, selected as a candidate miRNA, was down-regulated compared to its parental cells. In gain-of-function studies, *miR-99a-5p* inhibited cell viabilities, and restored sensitivity to gemcitabine. RNA sequencing analysis was performed to find the target gene of *miR-99a-5p*. *SMARCD1* was selected as a candidate gene. Dual-luciferase reporter assays showed that *miR-99a-5p* directly regulated *SMARCD1*. Loss-of-function studies conducted with si-RNAs revealed suppression of cell functions, and restoration of gemcitabine sensitivity. *miR-99a-5p* overexpression and *SMARCD1* knockdown also suppressed gemcitabine-resistant cells *in vivo*. Furthermore, β-galactosidase staining showed that *miR-99a-5p* induction and *SMARCD1* suppression contributed to cellular senescence. In summary, tumor suppressive *miR-99a-5p* induced cellular senescence in gemcitabine-resistant bladder cancer cells by targeting *SMARCD1.*