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REDUCTION OF INTRACELLULAR ATP CONTRIBUTES TO THE SUPPRESSIVE EFFECT OF CYT997 ON METASTASIS

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Treatment options for metastatic head and neck squamous cell carcinoma (HNSCC) are often limited and the 5-year survival rate has remained static and the development of more efficient but less toxic therapeutic strategies is an unmet need for treatment of more extensive HNSCC. Here, we report that CYT997, a novel microtubule-disrupting chemo drug, exerts strong activity in inhibiting HNSCC cell invasion and metastasis. The loss of invasion capacity by CYT997 was accompanied by an associated increase in cell adhesion and the reversal of epithelial-mesenchymal transition (EMT). Increased expression of E-cadherin protein and decreased expression of vimentin protein became evident in HNSCC cells following CYT997 exposure, which were consistently observed in HNSCC xenografts from the mice receiving CYT997. Moreover, the capacity of invasive HNSCC cells to form pulmonary metastases was significantly blocked with CYT997 treatment, indicating that the diminishment of EMT traits contributes to CYT997-suppressed metastasis. Intriguingly, CYT997 impaired intracellular ATP levels in HNSCC cells, at least in part, through its inhibitory effect on the mitochondrial protein IF1. The addition of ATP attenuated CYT997-induced suppression of cell invasion, coupled with down regulation of E-cadherin and upregulation of vimentin. These findings support a critical role of ATP levels in cell invasion and metastasis under the influence of CYT997. Collectively, our data unveil the mechanism involved in mediating CYT997 action and provide preclinical rationale for possible clinical application of CYT997 as a novel therapeutic strategy against aggressive HNSCC.

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