

Efflux Transporters Are Elevated and Microbially Regulated in Head and Neck Cancer

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Abstract

Background: Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 4% of cancer diagnoses and was projected to cause 16,680 US deaths in 2025. Major risk factors include tobacco and alcohol use and high-risk human papillomavirus (HPV) infection. Although chemotherapy remains important for HNSCC treatment, its effectiveness can be limited by efflux transporters that remove drugs from cancer cells. Currently, the levels of drug efflux transporters in HNSCC remain poorly characterized. We aimed to examine the levels of efflux transporters in HNSCC and identify if oral microbes were capable of impacting efflux activity. **Methods & Results:** We analyzed gene expression data from The Cancer Genome Atlas (TCGA) to determine the expression of drug efflux transporters in HNSCC. We found that drug efflux transporters ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, and ABCG1 were increased in the HNSCC tumors compared to control tissues. We chose to focus on ABCC2, which encodes the drug efflux transporter MRP2, since it is known to transport several chemotherapy drugs out of cancer cells. We found that ABCC2 expression was elevated in tumors from patients with stage I-IV cancer, across all tumor grades (1-3), in both male and female patients, and across multiple racial groups, including Caucasian, African American, and Asian patients. Interestingly, ABCC2 expression was significantly higher in HPV-negative tumors, but not in HPV-positive tumors. To determine the bacteria found most commonly found in HNSCC, we examined the Bacteria in Cancer (BIC) Database. We found *Prevotella* was the top genera in HNSCC tumors, followed by *Fusobacterium* and *Streptococcus*. To determine if these bacteria affect MRP2 activity, we cultured multiple *Prevotella* and *Streptococcus* strains in a defined bacterial medium and applied cell-free bacterial supernatant to human CAL-27 tongue squamous cell carcinoma cells. MRP2 activity was measured using the fluorescent dye 5-(and-6)-carboxy-2',7'-dichlorofluorescein diacetate (CDCFDA), which is exported from cells by MRP2. We found that secreted compound from *P. intermedia* and *P. melaninogenica*, but not *S. oralis*, *S. salivarius*, *S. sanguinis*, *S. parasanguinis* or *S. gallyticus* altered CDCFDA efflux in CAL-27 cells. **Conclusions.** These findings suggest that bacteria in HNSCC could impact drug efflux activity.