OSCC is one of the top 10 causes of cancer deaths worldwide, with only a 50% 5-year survival rate, necessitating the discovery of novel biomarkers and therapeutic targets. Using cDNA microarray analyses, we identified expression of a panel of kallikreins (KLK 5, 7, 8, and 10) associated with formation of more aggressive OSCC tumors in a murine orthotopic OSCC model. The goal of the current study is to elucidate the function of KLKs in OSCC progression. In initial studies, KLK levels in malignant OSCC cells (SCC25) were compared to cells from normal oral mucosa (OKF/6) and pre-malignant oral keratinocytes (pp126) using qPCR. A marked elevation of all KLKs was observed in aggressive SCC25 cells relative to OKF/6 cells. In normal skin, KLKs 5, 7, and 8 are involved in desquamation during epidermal differentiation via proteolytic cleavage of the desmosomal cadherin component desmoglein 1 (Dsg1). As loss of cell-cell adhesion is prevalent in tumor metastasis, Dsg1 was evaluated by immunofluorescence and western blotting. SCC25 cells exhibit cleavage of Dsg1 which is blocked by treatment with a KLK inhibitor as well as by siRNA silencing of KLK5. Furthermore, cell-cell adhesion and barrier function assays demonstrate that silencing of KLK5 enforces cell-cell adhesion and improves epithelial barrier function. Current studies are focusing on overexpression KLK5 in normal oral mucosal cells (OKF/6) to further evaluate the role of KLK5 in desmosomal cadherin processing.