Pro-angiogenic tumor-stroma interactions in the feline oral squamous cell carcinoma microenvironment

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Feline oral squamous cell carcinoma (FOSCC) tumors contain heterogeneous cell types with variable access to oxygen and nutrients that may contribute to treatment resistance. Angiogenic inhibitors have shown promise as adjuvant therapies, but the response is non-curative and highly variable between patients. This study aimed to elucidate how cell signalling between cancer-associated fibroblasts and FOSCC cells impact tumor angiogenesis. To achieve this, feline tracheal fibroblasts (CRL6167) and gingival FOSCC cells (SCCF2) were grown in monocultures and cocultures for 72 hours in normoxic or hypoxic culture conditions. Relative mRNA expression of 4 vascular endothelial growth factor (*VEGF*) genes, *VEGF-A, -B, -C*, and *-D*, was evaluated using reverse transcription- quantitative PCR (RT-qPCR). Inflammatory contributors to angiogenesis were also evaluated using RT-qPCR to measure *COX2* and *PTGES1* expression, and a commercial enzyme linked immunosorbent assay (ELISA) kit assessed PGE2 production. Coculture increased inflammatory PGE2 abundance in fibroblasts in both oxygen concentrations, but this change was not reflected in inflammatory mRNA expression. While coculture did not produce statistically significant differences in *VEGF* expression, hypoxia contributed significantly to decreased expression of *VEGF-C* in fibroblasts grown with fibroblasts as well as decreased *VEGF-D* expression in FOSCC cells grown with fibroblasts. These results suggest FOSCC cells may contribute to stromal inflammation through paracrine cell signaling, but the effect of chronic hypoxia on angiogenesis may be less reliable.

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