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# Investigation of Vascular Endothelial Growth Factor-A and Its Receptor in Canine Prostate Cancer

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**Abstract**

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) represent a complex family of angiogenic molecules, consisting of different ligands and different receptors. In both physiological and pathological processes, VEGFR2 receptor triggers angiogenesis after stimulation by VEGFA. In different human and canine tumors, cancer cells can express both VEGFR2 and VEGFA in a self-stimulation loop, resulting in angiogenesis and cell proliferation. Due to the importance of VEGF/VEGFR signaling in tumor proliferation and angiogenesis, this study aimed to evaluate VEGFA and VEGFR-2 protein and gene expression in canine prostate cancer (PC). We analyzed 12 normal prostates (NP), 12 proliferative inflammatory atrophy (PIA) lesions and 30 canine PC from the archives of the Sao Paulo State University and The University of Queensland. Protein expression and gene expression were evaluated by immunohistochemistry and RT-qPCR, respectively. The immunohistochemical staining for VEGFA and VEGFR-2 was quantified using a selected threshold from the Image J Software. The gene expression was evaluated comparing relative quantification (RQ). The survival curve was calculated for PCs using the Kaplan-Meier method, and the statistical significance was determined using a log-rank test. PC samples were classified according to the Gleason score (GS) in low GS tumors (scores 6 and 7) and high GS tumors (score 8, 9 and 10). A negative to weakly positive VEGF and VEGFR expression was observed in the epithelial cells of NP and PIA. On the other hand, canine PC expressed higher VEGF ($P<0.0001$) and VEGFR ($P<0.0001$) compared to normal samples. Regarding VEGF and VEGFR gene expression, we did not find significant statistical differences in all comparisons. A positive correlation between VEGF and VEGFR gene expression (Spearman $r= 0.68$ and $P=0.013$) and between VEGF and VEGFR protein expression (Spearman $r= 0.8$ and $P<0.0001$) was also observed in normal samples. This correlation was lacking in PC samples. Interestingly, we identified higher VEGF and VEGFR gene and protein expression in tumors with high Gleason score compared to the low GS group. Additionally, PC-affected patients with higher VEGFR expression experienced a lower survival time ($P=0.0372$) compared to patients with low VEGFR expression. In conclusion, VEGFR seems to be an independent prognostic factor in animals with prostate cancer.

**Keywords:**

VEGFA,

VEGFR-2,

Angiogenesis,

Prostate,

Dog Model.