Expression of vascular endothelial growth factor and its receptors in canine mast cell tumors

（犬の皮膚肥満細胞腫における血管内皮増殖因子およびその受容体の発現）

Abstract of Doctoral Thesis

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The aim of this thesis is to clarify the involvement of vascular endothelial growth factor (VEGF) -A and its receptors (VEGFRs; Flk-1 and Flt-1) in the differentiation and malignant progression of canine cutaneous mast cell tumors (MCTs). Immunohistochemical examinations revealed that expression of VEGF-A and Flk-1 in MCTs were associated with histological malignancy of the MCTs determined by histological grading systems and c-Kit patterns. In particular, VEGF-A/Flk-1 co-expression was found in highly malignant MCTs, indicating the involvement of their autocrine signaling to the MCT malignancy. Most of MCT cells expressing Flk-1 and/or VEGF-A also showed poor staining for safranin O (SO) and negative for Gi1 immunohistochemistry. These findings suggest that VEGF-A/Flk-1 signaling maintain the immature state of the tumor cells, which lead to the malignant progression in canine cutaneous MCTs. In normal skin mast cells (MCs) of rats, VEGF-A, Flk-1, and Flt-1 were expressed only in the immature cells during differentiation and maturation. Thus, VEGF-A/Flk-1 and VEGF-A/Flt-1 signaling may regulate the MC differentiation in a coordinated manner. The *in vitro* study using mouse bone-marrow derived MCs (mBMMCs) revealed co-expression of *vegf-A* and *flk-1* at the early, but not late stages of culture. In contrast, *gata2* expression increased at late stages of culture. Inhibition of Flk-1 signaling also upregulated *gata2* expression in the mBMMCs. These findings indicate that VEGF-A/Flk-1 signaling suppress MC differentiation and maintain phenotypes of immature MCs by downregulation of GATA2 expression. In conclusion, my thesis suggested that VEGF-A/Flk-1 signaling maintain the immature features by inhibition of GATA2, which lead to tumor progression in canine cutaneous MCTs. progression. Treatment targeted at VEGF-A/Flk-1 signaling would provide a new therapeutic strategy of the highly malignant MCTs.