Studies on the development of resistance to imatinib in canine mast cell tumor

(犬の肥満細胞腫におけるイマチニブ耐性化に関する研究)

Abstract

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Imatinib has been shown to have anti-tumor activity against canine MCT with KIT mutation; however, the tumors eventually develop resistance to imatinib in the most of the cases. Although acquiring resistance to imatinib is of the critical issues in the treatment of MCT in dogs, molecular mechanisms of imatinib resistance have not been investigated. The purpose of this study is to clarify the molecular mechanisms of imatinib resistance in MCT.

Nucleotide sequences of *KIT* were examined in six dogs with MCT that acquired imatinib resistance. In addition to the primary mutation in *KIT*, 1/6 dog had a second mutation in *KIT* (c.2463T>A, p.Asp815His). In contrast, five dogs did not have second mutation in *KIT*.

Imatinib resistant sub-lines (rCoMS1, IC50 = 9.0 μM; rVI-MC1, IC50 = 1.86 μM; rVI-MC10, IC50 = 12.2 μM) were then established from imatinib sensitive MCT cell lines CoMS and VI-MC, and the mechanisms of acquiring resistance to imatinib were investigated. Overexpression of KIT that was caused by retardation of KIT degradation via inhibition KIT ubiquitination by imatinib was identified in rCoMS1. Both in rVI-MC1 and rVI-MC10, a second mutation was found in *KIT*. Phosphorylation of the KIT with the second mutation was considerably less sensitive to imatinib. Moreover, KIT/SFK-independent activation of ERK was found in rVI-MC10.

In conclusion, the frequency of second mutation in *KIT* could be low in imatinib resistant canine MCT. Overexpression of KIT is one of a cause of acquiring resistance to imatinib in the cases without the second mutation in *KIT*. In the cases that have a second mutation in *KIT*, the second mutation was shown to be a cause of the resistance.

Moreover, KIT/SFK-independent activation of ERK would be involved in imatinib resistance when the neoplastic cells are exposed to higher concentrations of imatinib.