Studies on growth inhibitory effects of dasatinib against canine histiocytic sarcoma cell lines

Abstract

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Canine histiocytic sarcoma is an aggressive, often lethal tumor that arises from the histiocytic lineage including macrophages and dendritic cells. Although surgical excision and chemotherapy are used in the treatment of HS, the efficacy of these treatments is not enough. Therefore, a new therapeutic approach is required for the treatment of HS.

In the many types of tumors, living and growth of tumor is complexly related to varied abnormal molecular mechanisms. It is difficult to obtain powerful anti-tumor effects with inhibition of single abnormal molecular mechanism in these types of tumor. Currently, it has been recognized that living and growth in some types of tumor are depended on an abnormal signal transduction resulted in an abnormality of single molecular. In these tumors, molecular target drug shows marked anti-tumor effects with selectively inhibition of single abnormal molecular. In the past, specific molecular mechanism which strongly regulates living and growth of HS has not been detected. Therefore, molecular target therapy against canine HS still has not been established.

From here, to establish molecular target therapy against canine HS, we first searched for candidate compounds which have growth inhibitory effect to CHS-1 and MHT-2 cells. dasatinib was identified as an inhibitor to growth of CHS-1 cells. Moreover, dasatinib clearly inhibited the growth of four out of six HS cell lines. In this study, growth in some subset of HS cells is depended on some kind of kinase targeted by dasatinib. Herein, dasatinib showed growth inhibitory effect to these types of HS cells.

Secondly, From the result of analysis of well-known targeting molecular of dasatinib, no aberrance of gene and no activation of downstream signaling pathway in these molecular in dasatinib sensitive HS cell lines. As the result of exhaustive phosphorylated protein analysis in CHS-1 cells, it seemed that growth of CHS-1 cells is strongly regulated by constant phosphorylation of 14-3-3 protein gamma and the growth inhibitory effect of dasatinib in CHS-1 cells is caused by stopping of cell cycle progression resulted in inhibiting phosphorylation of 14-3-3 protein gamma.

Finally, we evaluated the effect of dasatinib *in vivo* using CHS-1 xenograft mouse model. It was apparent that dasatinib clearly inhibited the growth of xenografted tumors *in vivo*. It seemed that this growth inhibitory effect of dasatinib may be caused by inhibition of cell division and promotion of cell death

In conclusion, our study suggested that a constant phosphorylation of 14-3-3 protein gamma plays a crucial role in the growth of some specific type of HS cells. Dasatinib showed growth inhibitory effects in HS cells with prolonged phosphorylation of 14-3-3 protein gamma both *in vitro* and *in vivo.* Therefore, dasatinib has potent efficacy for the treatment in the selected clinical HS cases with constant phosphorylation of 14-3-3 protein gamma in these tumor cells.