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Oncogenic c-kit transcript is a target for binase

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Abstract

Mutational activation of c-Kit receptor tyrosine kinase is common in acute myelogenous leukemia. One such activating point mutation is the N822K replacement in the c-Kit protein. Here we investigate the selective cytotoxic effect of binase - RNase from Bacillus intermedius - on FDC-P1-N822K cells. These cells were derived from myeloid progenitor FDC-P1 cells, in which ectopic expression of N822K c-kit gene induces interleukin-3 independent growth. In order to determine whether the sensitivity of these cells to binase is caused by the expression of c-kit oncogene, the cytotoxicity of the RNase was studied in the presence of selective inhibitor of mutated c-Kit imatinib (Gleevec). Inhibition of mutated c-Kit protein leads to the loss of cell sensitivity to the apoptotic effect of binase, while the latter still decreases the amount of cellular RNA. Using green fluorescent protein as an expression marker for the c-Kit oncoprotein, we demonstrate that the elimination of c-Kit is the key factor in selective cytotoxicity of binase. Quantitative RT-PCR with RNA samples isolated from the binase-treated FDC-P1-N822K cells shows that binase treatment results in 41% reduction in the amount of c-kit mRNA. this indicates that the transcript of the activated mutant c-kit is the target for toxic action of binase. Thus, the combination of inhibition of oncogenic protein with the destruction of its mRNA is a promising approach to eliminating malignant cells. © 2010 Landes Bioscience.

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Keywords

Cellular RNA degradation, Cytotoxic RNase, Imatinib (gleevec), Interleukin, Mutated c-Kit, Myeloid progenitor cells, Oncogene expression