عنوان مقاله:

Differences in growth promotion, drug response and intracellular protein trafficking of FLT۳ mutants

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خلاصه مقاله:

Objective(s): Mutant forms FMS-like tyrosine kinase-۳ (FLT۳), are reported in ۲۵% of childhood acute lymphoid leukemia (ALL) and ۳۰% of acute myeloid leukemia (AML) patients. In this study, drug response, growth promoting, and protein trafficking of FLT۳ wild-type was compared with two active mutants (Internal Tandem Duplication (ITD)) and D۸۳۵Y. Materials and Methods:FLT۳ was expressed on factor-dependent cells (FDC-P۱) using retroviral transduction. The inhibitory effects of CEP۷۰۱, imatinib, dasatinib, PKC۴۱۲ and sunitinib were studied on cell proliferation and FLT۳ tyrosine phosphorylation. Total expression and proportion of intracellular and surface FLT۳ was also determined. Results: FDC-P۱ cells became factor-independent after expression of human FLT۳ mutants (ITD and D۸۳۵Y). FDC-P۱ cells expressing FLT۳-ITD grow ۳ to ۴ times faster than those expressing FLT۳-D۸۳۵Y. FD-FLT۳-ITD cells were three times more resistant to sunitinib than the FD-FLT۳-WT cells. The Geo means for surface FLT۳ expression in FD-FLT۳-ITD and –D۸۳۵Y were ۶۵ and ۷۰% less than the FD-FLT۳-WT cells. About ۴۰% of expressed FLT۳ was detected as intracellular in FD-FLT۳-D۸۳۵Y cell compared to ۴ and ۴.۵% in FD-FLT۳-WT and –ITD cells. Conclusion: Retention of D۸۳۵Y FLT۳ mutant protein may cause altered signaling, endoplasmic reticulum stress and activation of apoptotic signaling pathways leading to lower proliferation rate in FD-FLT۳-D۸۳۵Y than the FLT۳-WT and ITD mutant., these may also also contribute, along with the preferential affinity, to the increased sensitivity of D۸۳۵Y of CEP۷۰۱ and PKC۴۱۲. Studying these genetic variations can help determining the prognosis and designing a therapeutic plan for the patients with FLT۳ mutations.

کلمات کلیدی:

Activating mutation, Drug response, FLT۳, Protein trafficking