Identification of a novel type of ITD mutations located in nonjuxtamembrane domains of the FLT3 tyrosine kinase receptor.

Abstract: In acute myeloid leukemia (AML), internal tandem duplications (ITDs) of the juxtamembrane (JM) of FLT3 have been shown to play a crucial role in driving proliferation and survival of the leukemic clone. Here, we report the identification of FLT3_ITD mutations located in non-JM domains of the FLT3-receptor. This novel type of FLT3_ITD mutation was found in 216 of 753 (28.7%) of unselected FLT3_ITD-positive AML cases. An FLT3 receptor harbouring a prototypic non-JM ITD (FLT3_ITD627E) mediated constitutive phosphorylation of FLT3 and of STAT5, suggesting that non-JM ITDs confer constitutive activation of the receptor. FLT3_ITD627E induced transformation of hematopoietic 32D cells and led to a lethal myeloproliferative disease in a syngeneic mouse model. Our results indicate that a significant proportion of activating FLT3_ITD mutations is not confined to the JM domain of FLT3. Further studies are warranted to define the biologic and clinical characteristics of non-JM ITDs.

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