Dokumenttyp: journal article

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Titel des Beitrags: CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes.

Abstract: PURPOSE: CBL is a negative regulator of activated receptor tyrosine kinases (RTK). In this study, we determined the frequency of CBL mutations in acute leukemias and evaluated the oncogenic potential of mutant CBL. EXPERIMENTAL DESIGN: The cDNA of 300 acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) and acute lymphoblastic leukemia (ALL) patients and 82 human leukemic cell lines was screened for aberrations in the linker and RING finger domain of CBL. The oncogenic potential of identified mutants was evaluated in hematopoietic cells. RESULTS: We identified 3 of 279 AML/MDS patients expressing CBL exon 8/9 deletion mutants. Three of four cases at diagnosis expressed deleted transcripts missing exon 8 or exon 8/9. In remission samples a weak or no expression of mutant CBL was detected. No aberrations were found in normal hematopoietic tissues. One of 116 sequenced AML/MDS cases carried a R420G missense mutation. All AML/MDS patients with identified CBL mutants belonged to the core binding factor and 11q deletion AML subtypes. Functionally, CBL negatively regulated FMS-like tyrosine kinase 3 (FLT3) activity and interacted
with human FLT3 via the autophosphorylation sites Y589 and Y599 and colocalized in vivo. Expression of CBLDeltaexon8 and CBLDeltaexon8+9 in FLT3-WT-Ba/F3 cells induced growth factor-independent proliferation associated with autophosphorylation of FLT3 and activated the downstream targets signal transducer and activator of transcription 5 (STAT5) and protein kinase B (AKT). FLT3 ligand-dependent hyperproliferation of CBL mutant cells could be abrogated by treatment with the FLT3 PTK inhibitor PKC412 (midostaurin). CONCLUSION: CBL exon8/9 mutants occur in genetically defined AML/MDS subtypes and transform hematopoietic cells by constitutively activating the FLT3 pathway. This phenotype resembles the one of mutated RTKs and suggests that CBL mutant AML patients might benefit from treatment with FLT3 PTK inhibitors.

Zeitschriftentitel / Abkürzung:
Clin Cancer Res

Jahr: 2009
Band: 15
Heft / Issue: 7
Seiten: 2238-47
Sprache: eng
Print-ISSN: 1078-0432
TUM Einrichtung:
III. Medizinische Klinik und Poliklinik

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > III. Medizinische Klinik und Poliklinik (Hämatologie / Onkologie) > 2009

entries: