Cooperation of BRAF(F595L) and mutant HRAS in histiocytic sarcoma provides new insights into oncogenic BRAF signaling.

Activating BRAF mutations, in particular V600E/K, drive many cancers and are considered mutually exclusive with mutant RAS, whereas inactivating BRAF mutations in the D(594)F(595)G(596) motif cooperate with RAS via paradoxical MEK/ERK activation. Due to the increasing use of comprehensive tumor genomic profiling, many non-V600 BRAF mutations are being detected whose functional consequences and therapeutic actionability are often unknown. We investigated an atypical BRAF mutation, F595L, which was identified along with mutant HRAS in histiocytic sarcoma and also occurs in epithelial cancers, melanoma and neuroblastoma, and determined its interaction with mutant RAS. Unlike other DFG motif mutants, BRAF(F595L) is a gain-of-function variant with intermediate activity that does not act paradoxically, but nevertheless cooperates with mutant RAS to promote oncogenic signaling, which is efficiently blocked by pan-RAF and MEK inhibitors. Mutation data from patients and cell lines show that BRAF(F595L), as well as other intermediate-activity BRAF mutations, frequently coincide with mutant RAS in various cancers. These data define a distinct class of activating BRAF mutations, extend the spectrum of
patients with systemic histiocytoses and other malignancies who are candidates for therapeutic blockade of the RAF-MEK-ERK pathway and underscore the value of comprehensive genomic testing for uncovering the vulnerabilities of individual tumors.

Zeitschriftentitel / Abkürzung:
Leukemia

Jahr:
2016

Band:
30

Heft / Issue:
4

Seiten:
937-46

Sprache:
eng

Volltext / DOI:
http://doi.org/10.1038/leu.2015.319

Pubmed:

Print-ISSN:
0887-6924

TUM Einrichtung:
Institut für Allgemeine Pathologie und pathologische Anatomie

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Allgemeine Pathologie und Pathologische Anatomie > 2016
- Hochschulbibliographie > 2016 > Fakultäten > Medizin > Institut für Allgemeine Pathologie und Pathologische Anatomie

entries: