Unconventional EGF signal, EGF-KITENIN/ErbB4-AP-1 axis can confer resistance to cetuximab in colorectal cancer

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Approximately 20% of metastatic colorectal cancer (CRC) patients who show no response to anti-EGFR targeted therapies do not harbor mutations in KRAS, BRAF, and PIK3CA, nor loss of PTEN expression. Previously, we identified KITENIN (KAI1 C-terminal interacting tetraspanin) as a metastasis-enhancing gene and found it to be highly expressed in sporadic CRC tissues. We recently found that EGF further increases invasiveness of KITENIN-transfected CRC cells via KITENIN/ErbB4-c-Jun axis. Here we investigated whether this novel EGF function endows CRC cells expressing higher KITENIN with enhanced survival in response to cetuximab. HCT116 and Caco2 CRC cells expressing higher KITENIN were more resistant to cetuximab than were DLD1 and SW620 CRC cells expressing lower KITENIN. The highly KITENIN-expressing Caco2 cells, a KRAS/BRAF wild-type cell line, were resistant to cetuximab, whereas KITENIN-knockdown Caco2 cells showed increased sensitivity. In DLD1 and HCT116 cells, mutant KRAS/BRAF cell lines, highly KITENIN-expressing DLD1 cells were resistant to cetuximab, whereas KITENIN-knockdown HCT116 cells showed sensitivity to cetuximab. The immunohistochemical expression of KITENIN was great in tumor tissues from metastatic CRC patients who showed progression of disease at initial stages after treatment with cetuximab, compared to those who exhibited a partial response. Overall, these results indicated that KITENIN/ErbB4-c-Jun axis could be a molecular basis for conferring resistance to anti-EGFR agents in CRC tissues in which KITENIN is highly expressed and that lower KITENIN levels in resected tumor tissues from metastatic CRC patients as a useful marker for identifying patients who would benefit from anti-EGFR targeted therapies.