Twisted kiss: in vitro and in vivo evidence of genetic variation and suppressed transcription of the metastasis-suppressor gene KiSS1 in early breast cancer.

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Source

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Abstract

KiSS-1 is ametastasis suppressor gene, its inactivation linked to advanced tumor stage and dismal prognosis. We studied its mutational status ,transcription and protein expression in human cancer cell lines and patients with early breast cancer.
Tumor tissue DNA and messenger RNA (mRNA) of KiSS1 exons III and IV from the human cancer cell lines Hela, Jurkat, A549, W138t, MCF-7 and from formalin-fixed resected breast adenocarcinomas from 50 women were analysed by means of PCR-SSCP, RT-PCR and sequencing. Tumor tissue was stained for KiSS1 protein expression by means of the streptavidin-biotin complex immunoperoxidase assay. Presence of KiSS1 mutation, mRNA levels and protein staining were examined for correlations with patient/tumor characteristics.
A transversion in exon IVa replacing cytosine with guanine was identified 242 base pairs from the translation start site (242C>G) in the cell lines MCF-7, A549 and in 5/50 tumors (10%), resulting in substitution of proline by arginine (P81R) and alteration of the protein tertiary structure. As the substitution was present in germ-line DNA in 3/5 breast cancer patients harbouring the polymorphism in their tumor, the incidence of tumour-specific somatic mutation was 4% among the 50 patiens with early breast cancer. Although the P81R substitution was associated with reduced KiSS1 protein immunoreactivity (56% in wild-type tumors versus 20% in KiSS1-variant tumours) and with axillary nodal involvement (55% in wild-type versus 80% in KiSS1-variant tumors), the correlations did not reach statistical significance. KiSS1 mRNA was detected in only 15/48 tumours (31%) and showed no correlation with mutation or protein expression. Twenty-six tumors stained for KiSS1 protein, in contrast to the universal strong staining seen in normal breast parenchyma and placental tissues. At amedian follow-up of 38 months, relapses occurred in 20% of women with non wild-type tumors versus 13% of women with wild-type KiSS1 tumors (p=0.7). Presence of KiSS1 mutation, mRNA levels and protein expression did not have prognostic significance for relapse-free survival.
In conclusion, altered nucleotide sequence and repression of transcription are two potential mechanisms of suppression of the anti-metastatic effects of KiSS1 in early breast cancer: Confirmation in larger cohorts and study of functional effects of the 242C>G exon IVa mutation are warranted. Keywords: KiSS1, metastasis-suppressor gene, breast cancer, mutation, transcription.