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The False Paradigm of RUNX3 Function as Tumor Suppressor in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) is a major cause of cancer mortality. GC studies that aim to identify relevant oncogenes and tumor suppressor genes (TSGs) are essential for devising effective new therapies. A decade ago, RUNX3, a gene that resides on human chromosome 1p36.1, was claimed to be a major TSG in GC. Since then, hundreds of studies involving thousands of GC patients have attempted to verify and extend the RUNX3 TSG paradigm. However, RUNX3 is not recognized as TSG and not listed in the "Cancer Gene Census" website. To be a TSG that protects normal cells against malignancy, the gene must be expressed in the normal tissue from which the cancer arose and its loss or inactivation should contribute to cancer development. This review summarizes compelling body of evidence challenging the RUNX3-TSG paradigm. Studies show unequivocally that RUNX3 is not expressed in normal gastric epithelium and that it fails to fulfill all other premises of a TSG. RUNX3 mutations and 1p36 deletions are not frequent in GC and RUNX3 is not associated with familial GC or with increased risk of GC. Accordingly, Runx3-/- mice do not develop tumors. RUNX3 promoter methylation, which has been reported to be a frequent event in GC, is not relevant to its alleged TSG function, since the gene is already silent in normal gastric epithelium. In sharp contrast, overexpression of RUNX3 was found in several types of human cancers, including GC, and the 1p36.1 region is amplified in B-cell lymphoma. Thus, it is possible that RUNX3 actually promotes cancer development rather than being a TSG. The true targets for GC therapy are discussed below. Those are genes frequently lost or amplified in GC and are well known for their tumor suppressive or oncogenic activity, respectively.

KEYWORDS

Gastric Cancer; RUNX3 Expression; Tumor Suppressor Genes; Promoter Methylation; Therapeutic Targets

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