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HIPK2 deficiency causes chromosomal instability by cytokinesis failure and increases tumorigenicity.

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Abstract

HIPK2, a cell fate decision kinase inactivated in several human cancers, is thought to exert its oncosuppressing activity through its p53-dependent and -independent apoptotic function. However, a HIPK2 role in cell proliferation has also been described. In particular, HIPK2 is required to complete cytokinesis and impaired HIPK2 expression results in cytokinesis failure and tetraploidization. Since tetraploidy may yield to aneuploidy and chromosomal instability (CIN), we asked whether unscheduled tetraploidy caused by loss of HIPK2 might contribute to tumorigenicity. Here, we show that, compared to Hipk2+/+ mouse embryo fibroblasts (MEFs), hipk2-null MEFs accumulate subtetraploid karyotypes and develop CIN. Accumulation of these defects inhibits proliferation and spontaneous immortalization of primary MEFs whereas increases tumorigenicity when MEFs are transformed by E1A and Harvey-Ras oncogenes. Upon mouse injection, E1A/Ras-transformed hipk2-null MEFs generate tumors with genetic alterations resembling those of human cancers derived by initial tetraploidization events, such as pancreatic adenocarcinoma. Thus, we evaluated HIPK2 expression in different stages of pancreatic transformation. Importantly, we found a significant correlation among reduced HIPK2 expression, high grade of malignancy, and high nuclear size, a marker of increased ploidy. Overall, these results indicate that HIPK2 acts as a caretaker gene, whose inactivation increases tumorigenicity and causes CIN by cytokinesis failure.

KEYWORDS:

CIN; HIPK2; cytokinesis failure; near-tetraploidy; tumorigenicity