Expression of the mitotic checkpoint gene MAD2L2 has prognostic significance in colon cancer.

Abstract:
Aneuploidy and genetic instability are a hallmark of colorectal cancer and other solid tumors, and they are thought to enhance tumor progression. The gene MAD2L2 (mitotic arrest deficient 2-like 2) encodes the spindle checkpoint protein MAD2L2 (or MAD2B), a key component of a surveillance system that delays anaphase until all chromosomes are correctly oriented. Defects in this mitotic checkpoint are known to contribute to genetic instability, i.e., numerical and structural aberrations of chromosomes. We have previously identified MAD2L2 as significantly upregulated in locally restricted colorectal tumors by gene expression profiling. So far, MAD2L2 has not been reported to play a major role in human cancer in contrast to its homologue MAD2. To address this question, 118 histologically confirmed colorectal lesions were analyzed by quantitative real-time PCR for expression of MAD2L2, and compared to normal colon tissue from 11 patients. Twenty-five out of 118 tumor samples (21%) showed MAD2L2 overexpression of 3-fold or more compared to normal colon, and the fraction of overexpressing tumors increased with tumor stage. Correspondingly, protein levels of MAD2L2 were found to be significantly upregulated in tumors as compared to matched normal tissue. Tumors with upregulated MAD2L2 expression had significantly higher numbers of
aberrant mitotic figures (anaphase bridges), an indication of chromosomal instability. Elevated expression of MAD2L2 was significantly correlated with reduced patient survival. By multivariate analysis, MAD2L2 expression was retained as an independent prognostic parameter for patient survival. Thus, our results demonstrate that overexpression of MAD2L2 correlates with bad prognosis in colorectal cancer.