Oncogenic β-catenin and MMP-7 cosegregate in late-stage clinical colon cancer

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Recent *in vitro* studies demonstrated that β-catenin translocated into the tumor cell nucleus functions as an oncogene by transactivating oncogenes, including MMP-7. We conducted a large-scale analysis of β-catenin and MMP-7 expression in human colon cancer to determine the potential clinical importance of these molecules. In 202 colon cancer patients with known post-operative outcomes, we determined the expression of β-catenin and MMP-7 in the tumors immunohistochemically and correlated the findings with the patients' clinicopathological characteristics and survival. We found two distinct patterns of β-catenin nuclear accumulation (NA) in the colon cancers: diffuse NA (NAd) in 89 cases (44%) and selective NA at the invasion front (NAinv) in 18 cases (9%). The presence of the NAinv pattern was significantly correlated with advanced Dukes' stage (P=0.0187) and tumor recurrence (P=0.0005) as well as with MMP-7 expression in the tumor invasion front (P=0.0025) (Figure 1), resulting in extremely unfavorable clinical outcomes (Figure 2). A multivariate analysis determined that the NAinv expression pattern and Dukes' C stage were independent prognostic factors. Oncogenic activation of β-catenin in the tumor invasion front, as represented by its NAinv pattern of expression, may be an independent and reliable indicator of membership in a subset of colon cancer patients who are highly susceptible to tumor recurrence and have a less favorable survival rate.

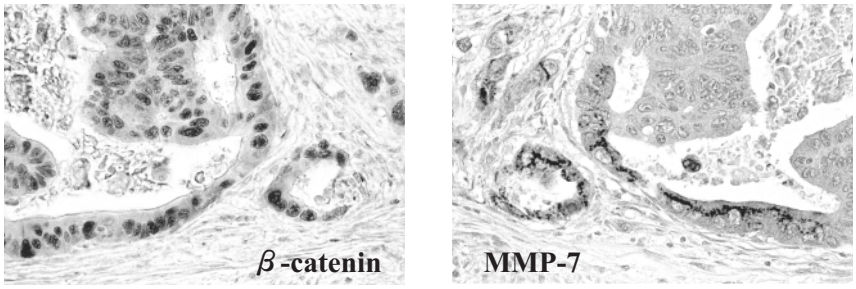

Figure 1. Immunohistochemical staining of a pair of serial sections from the same tumor in a mirror image clearly demonstrated colocalization of nuclear β-catenin and cytoplasmic MMP-7 in the same carcinoma cells in the invasion front.

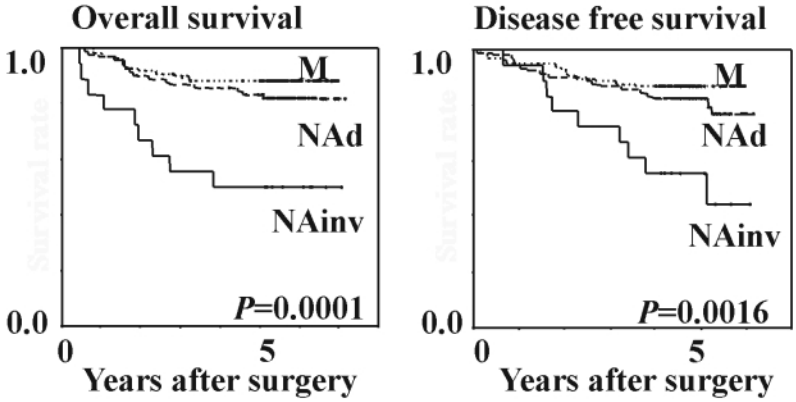

Figure 2. Comparison of survival of the patients with colon cancer according to the different patterns of β-catenin activation in the primary tumors. Kaplan-Meier survival curves showed a statistically significant survival disadvantage in colon cancers with NAinv pattern of β-catenin activation.