Expression of osteopontin, a target gene of de-regulated Wnt signaling, predicts survival in colon cancer.

Abstract:
Osteopontin (OPN) is a secreted phosphoprotein, which has been reported to be associated with tumor progression in numerous solid tumors. In a previous transcriptome study on colorectal cancer, we identified the gene OPN among the most strongly up-regulated transcripts. OPN has been suggested as a putative target of Wnt signaling, but the molecular mechanism responsible for its aberrant transcription is not fully understood. We analyzed 13 normal colon tissues, 9 adenomas, 120 primary colon tumors, and 10 liver metastases by quantitative reverse-transcription PCR. OPN expression was strongly elevated in primary colon cancer and liver metastasis, but not in pre-cancerous lesions and UICC stage I tumors. Multivariate analysis established OPN expression as an independent prognostic parameter for overall survival. Moreover, high OPN expression identified a subgroup of patients with bad prognosis. Next, we determined immunohistochemically a correlation of OPN expression with aberrant beta-catenin staining, which is indicative of Wnt activation. Elevated expression of OPN was significantly correlated with increased cytoplasmic and nuclear beta-catenin staining. The in vivo role of Wnt signaling for the expression of OPN was tested in genetically defined mouse models with (Apc(1638N)) or without (pvillin-KRAS(V12G)) Wnt
activating mutations. Mutation of the tumor suppressor APC was necessary for upregulation of OPN expression in the murine tumors on transcript and on protein levels. Thus, OPN is a transcriptional target of aberrant Wnt signaling, and OPN expression alone predicts survival in human colon cancer.