A SMAD4-modulated gene profile predicts disease-free survival in stage II and III colorectal cancer

Abstract

Loss of SMAD4, the central node in the TGF-β superfamily, has been associated with worse colorectal cancer outcomes. SMAD4 suppresses Wnt activity by repressing β-catenin via upregulation of the bone morphogenetic protein (BMP) arm of the pathway. We used gene ontology and bioinformatics tools to identify a SMAD4-modulated transcriptional profile associated with high-risk CRC. Using a two-stage approach, we analyzed BMP/Wnt genes for significant association with SMAD4 using a discovery dataset from 250 CRC patients. We then examined the BMP/Wnt genes for SMAD-binding elements (SBEs) in the promoter regions and association with SMAD4 expression levels. This approach implicated 15 genes. The prognostic utility of the SMAD4-modulated profile was evaluated by unsupervised hierarchical clustering in independent training and validation datasets. In the full training dataset (566 patients), the SMAD4 profile was not associated with outcome. However, among stage II and III patients (n=461), distinct clusters identified by unsupervised hierarchical clustering demonstrated significant association with disease-free survival in Kaplan-Meier analysis. Selected targets were validated using in vitro models of human CRC. Utilizing an independent dataset of 257 stage II and III patients, we validated a prognosis model identifying low- and high-risk groups of patients based on clusters from the training dataset. The SMAD4-modulated gene profile characterized in this study has potential for diagnostic and prognostic use in CRC patients.