Inhibition of S100A4-induced tumor growth and metastasis by intervening β-catenin signaling

Ulrike Stein

Experimental and Clinical Research Center, Charité University Medicine Berlin, and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany. E-mail: ustein@mdc-berlin.de

Colon cancer metastasis is often associated with activation of the Wnt/β-catenin signaling pathway and high expression of the metastasis-inducing gene S100A4. We identified previously S100A4 as a transcriptional target of β-catenin and thus highlighted the importance of the interconnection of these cellular programs for colon cancer metastasis [1]. Intervention strategies targeting Wnt/β-catenin signaling might represent promising approaches to inhibit S100A4-induced tumor growth and metastasis in vivo. Here we report the effects of nonsteroidal anti-inflammatory drug (NSAID) sulindac sulphide, a known inhibitor of the Wnt/ β-catenin signaling pathway, on S100A4-induced tumor growth and metastasis on human colon cancer cells. We demostrate the knock down of S100A4 expression and S100A4 promoter activity by sulindac, associated with reduced S100A4-induced cell motility and invasiveness in vitro, as well as with inhibition of tumor growth and liver metastasis in vivo. Our data provide evidence that modulators of β-catenin signaling such as NSAIDs may offer potential as antimetastatic agents by interdicting S100A4 expression [2].

[1] Stein U, Arlt F, Walther W, Smith J, Waldman T, Harris ED, Mertins SD, Heizmann CW, Allard D, Birchmeier W, Schlag PM, Shoemaker RH. The metastasis-associated gene S100A4 is a novel target of β-catenin / T-cell factor (TCF) signaling in colon cancer. Gastroenterology (2006) 131:1486-1500

[2] Stein U, Arlt F, Smith J, Sack U, Herrmann P, Walther W, Lemm M, Fichtner I, Schlag PM, Shoemaker RH. Inhibition of S100A4-induced tumor growth and metastasis by sulindac. (2009) (submitted)