

The E3 ubiquitin-ligase Hakai as a novel target against EMT

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Abstract

The epithelial-mesenchymal transition (EMT) is a process with enormous relevance in tumor progression and metastasis, as well as in the acquisition of drug resistance. EMT is characterized by the loss of the epithelial phenotype and cell-substrate adhesions, and the acquisition of a motile and invasive mesenchymal phenotype. The most established marker of EMT is the loss of expression of E-cadherin, a tumor suppressor that mediates cell-cell adhesion in the epithelium. Hakai is an E3 ubiquitin-ligase protein that mediates E-cadherin ubiquitination, endocytosis, and finally degradation, altering cell-cell contacts. Moreover, Hakai is important for tumor progression in different carcinomas such as colorectal cancer where Hakai is gradually increased TNM stages compared to adjacent healthy tissues. We have identified a novel small-molecule inhibitor, named Hakin-1, directed against HYB domain of Hakai domain. We show its antitumor effect in vitro, by its action on the E-cadherin ubiquitination and degradation. Furthermore, Hakin-1 reduces colony formation, proliferation, invasion and migration of colon cancer cell lines. These results suggest the potential of Hakin-1 as an effective therapy to inhibit tumor growth and carcinoma progression.