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Proteomic characterization of the E3 ubiquitin-ligase Hakai: Biological insights and new therapeutic strategies in colon cancer

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Abstract

Carcinoma is the most common type of cancer and arises from epithelial cells. Transition from adenoma to carcinoma is associated with the loss of E-cadherin and, in consequence, the disruption of cell–cell contacts. E-cadherin loss is a hallmark of the epithelial-tomesenchymal transition (EMT) and a predictor of poor prognosis during tumor progression. Hakai is an E3 ubiquitin-ligase that mediates E-cadherin ubiquitination, endocytosis and consequent degradation. Although E-cadherin is the most established substrate for Hakai activity, other regulated molecular targets for Hakai may be involved in cancer cell plasticity during tumor progression. We employed an iTRAQ approach to explore novel molecular pathways involved in Hakai-driven EMT. Our results show that Hakai may have an important influence on cytoskeleton-related proteins, extracellular exosomeassociated proteins, RNA-related proteins and proteins involved in metabolism. Among Hakai-regulated proteins, we describe the heat shock protein 90 (Hsp90) chaperone complex. Hsp90 participates in the correct folding of its client proteins, allowing them to maintain their stability and activity. By immunoprecipitation, we present evidence that Hakai interacts with Hsp90 chaperone complex in several epithelial cells and demonstrate that is a novel Hsp90 client protein. Pharmacological inhibition of Hsp90 with geldanamycin results in the degradation of Hakai in a lysosome-dependent manner. Interestingly, geldanamycin-induced Hakai degradation is accompanied by an increased expression of E-cadherin and Annexin A2. We also show that geldanamycin suppresses cell motility at least in part through its action on Hakai expression. We propose Hakai as a new client protein of Hsp90 chaperone highlighting a new mechanism by which Hsp90 inhibitors may influence Hakai-mediated EMT process and colorectal cancer treatment.

Biography

Angélica Figueroa obtained her Degree in Biology at Complutense University of Madrid (Madrid, Spain) in 1997. She then obtained her PhD studies in 2002 in Molecular Biology at the Biomedical Research Institute in Madrid (Spain). In 2003, she moved to London as a postdoctoral fellow in the laboratory of Prof. Yasuyuki Fuyita at MRC Laboratory for Molecular Cell Biology (LMCB), University College London where she became interested in studying the epithelial cell plasticity program during tumor progression, metastasis and therapy resistance. In 2009, she established her own lab at the Instituto de Investigación Biomédica A Coruña (INIBIC, La Coruña) where she is Research Group Leader of the Epithelial Plasticity and Metastasis Group.