Nancy Gavert, J Cell Sci Ther 2011, 2:4
doi: http://dx.doi.org/10.4172/2157-7013.S1.02

OMICS Group Conferences
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International Conference & Exhibition on
Cell Science & Stem Cell Research

29 Nov - 1 Dec 2011 Philadelphia Airport Marriott, USA

L1 confers metastasis in colon cancer cells by activating NF-βB signaling independent of changes in EMT and cancer stem cell markers

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Aberrant activation of β-catenin-TCF gene expression is a common event in most human colorectal cancer (CRC) patients. Our studies have previously identified the neuronal cell adhesion receptor L1 as a target gene of β -catenin-T cell factor (TCF) signaling in CRC cells and tissue. L1 over-expressing human CRC cells are tumorigenic, and when injected into the spleen of mice, exhibited extensive liver metastasis. L1 is exclusively localized at the invasive front of human CRC tissue together with p65, a member of the NF- β B pathway, and ezrin, a submembrane molecule that links cell-surface receptors to the actin cytoskeleton. L1 can activate NF- β B by inducing the phosphorylation and degradation of I β B (the NF- β B inhibitor), by an interaction with ezrin. The knockdown of NF- β B activity and the suppression of ezrin levels, or a point mutation in the ezrin-binding site on the L1 cytodomain, abrogate L1-mediated metastasis. L1 can induce the activating phosphorylation of ezrin and its membranal co-localization with L1 and I β B. The L1-induced metastasis in CRC cells apparently does not include changes in epithelial to mesenchymal (EMT) markers, and no suppression of E-cadherin, or up-regulation of mesenchymal markers by L1 is observed. L1 levels also do not correlate with the expression of CRC stem cell (CSC) markers. Moreover, in CRC cells the up-regulation of Slug and Twist (key EMT mediators) while reducing E-cadherin and inducing fibronectin and vimentin, does not lead to metastasis. Our results indicate that L1 promotes metastasis in CRC cells by activating the NF- β B pathway but without changes in EMT and CSC markers.

Biography

Nancy Gavert received her M.D. from Hebrew University Medical School in 1995 and completed her residency in General Surgery in 2001. Eight years ago she decided to focus her attention on research and completed her Ph.D. and postdoctoral studies at the Weizmann Institute of Science. She is presently a staff scientist in the same institute and was first to describe L1 as a target of β-catenin and to show its importance in the development of colorectal cancer metastasis. She has since published a number of papers elucidating the role of L1 in colorectal cancer.