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The complex role of SHP-2 tyrosine phosphatase in the development of colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in the world. A major risk factor to develop CRC is the presence of chronic inflammation in the colon. But how chronic inflammation contributes to the development of CRC is not so clear. In seeking to answer this question, we have focused on the signaling molecule SHP-2, a tyrosine phosphatase modulating cellular signals induced by both growth factors and pro-inflammatory cytokines. Polymorphisms in the *PTPN11* locus encoding SHP-2 have been reported to be markers of colitis susceptibility. Conversely, gain-of-function mutations in *PTPN11* have recently been associated with sporadic CRC. To investigate the role of SHP-2 in intestinal homeostasis, we have generated mice with an intestinal epithelial cell (IEC)-specific deletion of its expression. We demonstrated that IEC disruption of SHP-2 causes severe chronic inflammation in the colon. This inflammatory phenotype is associated with a dramatic increase in proliferation and activation of Wnt/β-catenin, NFkB and STAT3 signaling in colonic epithelium. With age, these mice develop malignant lesions in the colon suggesting that SHP-2 can act as a tumor suppressor in this tissue. Furthermore, SHP-2 epithelial deficiency severely increased colon tumor load in $Apc^{min/+}$ mice. Aside from these observations, we found increased expression and activating mutations of SHP-2 in sporadic human colorectal tumors and SHP-2 silencing markedly attenuated KRAS-induced transformation of IECs in culture. Hence, this suggests that SHP-2 can act as an oncogene in the colonic epithelium. Opposing roles for SHP-2 in promoting and suppressing tumorigenesis in the large intestine are therefore proposed.

Biography

Nathalie Rivard has received her PhD from Université de Sherbrooke in 1994 and has completed her Post-doctorate at the Centre de Biochimie-CNRS, Université de Nice, in France in 1997. She has worked as a Faculty Member in the Department of Anatomy and Cell Biology at the Faculté de Médecine et des Sciences de la santé de l'Université de Sherbrooke. Her research focuses on the analysis of signaling pathways that control proliferation, differentiation, tumorigenesis and inflammatory response of intestinal epithelial cells. She has published more than 80 papers in reputed journals. She is the recipient of 2013 Canadian Association of Gastroenterology Research Excellence Award and holds a position of Canada Research Chair.

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