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Nathalie Rivard

Universite de Sherbrooke, Sherbrooke, Canada

Epithelial SHP-2 protects the intestinal mucosa against colitis and colorectal cancer

SHP-2 is a Src homology 2 containing protein tyrosine phosphatase (PTP) expressed in most embryonic and adult tissues. SHP-2 regulates many cellular functions including growth, differentiation, innate immune response, chemotaxis and survival. Genetic and biochemical evidence demonstrate that SHP-2 can regulate major signalling pathways including the RAS/MAPK, PI3K/Akt and JAK/STAT pathways. Interestingly, variations within the human gene locus encoding SHP-2 have been associated with increased susceptibility to develop ulcerative colitis. We thus, analyzed the role of SHP-2 in the intestine by first generating mice with an intestinal epithelial cell (IEC)-specific deletion of SHP-2 expression (SHP-$2^{IEC\text{-}KO}$ mice). Interestingly, these mice rapidly developed inflammation one month after birth, with clinical and histopathological features similar to ulcerative colitis. Alterations in Goblet/Paneth cell ratio were observed two weeks after birth, before the onset of inflammation and were associated with significant alterations in microbiota composition. With age, SHP-2 mice developed colitis-associated adenocarcinomas. To further analyze the protective role of SHP-2 in the intestinal epithelium, we also generated mice expressing a constitutive active form of SHP-2 specifically in IECs (SHP-$2^{IEC\text{-}E76K}$ mice). These mice were either challenged with dextran sulfate sodium (DSS) to induce chemical colitis or with *Citrobacter rodentium* to induce infectious colitis. Results showed that SHP-$2^{IEC\text{-}E76K}$ mice were resistant to DSS treatment or C. rodentium infection. Thus, SHP-2 activation exerts protective actions against mucosal damage and during infection with an A/E (attaching and effacing) bacterial pathogen. Finally, we found reduced SHP-2 expression in intestinal biopsies from patients with active colitis, emphasizing the inverse relationship between SHP-2 expression and colonic inflammatory phenotype. Overall, our results indicate that SHP-2 maintains barrier function in the colon and thereby, helps to prevent spontaneous microbiota-driven inflammation and colitis-associated cancer development.

Biography

Nathalie Rivard received her PhD from Universite de Sherbrooke in 1994 and completed a 3.5 year Post-doctorate at the Centre de Biochimie-CNRS, Université de Nice, France with Dr. J Pouysségur in 1997. Then, she accepted a faculty position in the Department of Anatomy and Cell Biology at the Faculté de Médecine et des Sciences de la santé de l'Université de Sherbrooke. Since 2008, she is the Chair of the Department of Anatomy and Cell Biology and Chair of the Cancer Axis at Université de Sherbrooke. Her research focuses on the analysis of signalling 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 Canada Research Chair.

Nathalie.Rivard@usherbrooke.ca