BMC Proceedings

POSTER PRESENTATION Open Access

Toll-Like Receptors are critical in controlling colonic inflammation and cancer

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From Institut Pasteur International Network Annual Scientific Meeting
Hong Kong. 22-23 November 2010

Despite the presence of large number and diverse populations of commensal microbes, gut mucosa has evolved to maintain "microbial-tolerance", which is critically regulated by well-controlled Toll-like receptor (TLR) signaling. Deregulated TLR signaling has been linked to the pathogenesis of inflammatory bowel disease and colon cancer; however, the underlying mechanisms need to be further defined. In this study, we uncovered that lack of SIGIRR, a negative regulator for TLR and IL-1R signaling, led to increased genetic instability and LOH of *Apc*, resulting in spontaneous colonic polyposis in $Apc^{min/+}/Sigirr^{-/-}$ mice. Importantly, elevated colonic tumorigenesis in $Apc^{min/+}/Sigirr^{-/-}$ mice is dependent on the presence of commensal microbes in gut, implicating a critical role for TLR signaling in tumorigenesis. Furthermore, we demonstrated that SIGIRR-modulated TLR-mediated tumor initiation is mainly through the activation of the Akt-mTOR axis, which promotes cell cycle progression through its impact on posttranscriptional control of the key cell cycle regulators (Cyclins, c-Myc and cdk2). Moreover, abrogation of mTOR pathway by rapamycin prevented microadenoma and polyps formation in $Apc^{min/+}/Sigirr^{-/-}$ mice, providing new insights into treating human cancers. In addition, augmented production of proinflammatory cytokines, such as IL-6 and IL-23, further promoted tumor growth in $Apc^{min/+}/Sigirr^{-/-}$ mice. Epithelium specific re-expression of SIGIRR in $Apc^{min/+}/Sigirr^{-/-}$ mice ameliorated intestinal tumorigenesis. In summary, this study indicates that SIGIRR is a critical tumor suppressor that controls tumorigenesis by inhibiting TLR-induced mTOR and NFkB pathways in colonic epithelium.

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Published: 10 January 2011

doi:10.1186/1753-6561-5-S1-P87
Cite this article as: Xiao *et al.*: Toll-Like Receptors are critical in controlling colonic inflammation and cancer. *BMC Proceedings* 2011 **5** (Suppl 1):P87.