Cross talk between prostaglandin E_2 and peroxisome proliferator-activated receptor δ signaling in inflammation and colorectal cancer

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Evidence for the link between inflammation and cancer comes from epidemiologic and clinical studies showing that use of nonsteroidal anti-inflammatory drugs (NSAIDs) protects against colorectal cancer (CRC) incidence and mortality. NSAIDs exert some of their anti-inflammatory and anti-tumor effects by targeting cyclooxygenase-2 (COX-2). COX-2-derived prostaglandin E_2 (PGE_2) is a pro-inflammatory mediator that promotes tumor progression. Another mechanism for the contribution of dietary fats to carcinogenesis has been focused on the members of the peroxisome proliferator-activated receptors (PPARs) family. Recent emerging evidence shows that PPARδ is involved in chronic inflammation and the progression of hereditary and sporadic CRC. Considering the importance of PGE_2 and PPARδ signaling in inflammation and colorectal carcinogenesis, the aim of our present study was to determine whether a cross talk between PGE_2 and PPARδ signaling contributes chronic inflammation and colitis-associated carcinogenesis.

Our previous study demonstrated that PPARδ mediated the effects of PGE_2 on promoting intestinal adenoma growth in $Apc^{min/+}$ mice. We further present evidence demonstrating that deletion of PPARδ diminished colonic inflammation and inhibited colitis-associated tumor growth accompanied with reducing infiltration of immune cells as well as the expression of pro-inflammatory chemokines and cytokines. Our results further reveal that activation of PPARδ induces COX-2 expression in colonic epithelial cells. Importantly, COX-2-derived PGE_2 stimulates macrophages to produce pro-inflammatory chemokines and cytokines. Collectively, our results demonstrate that PPARδ promotes colonic chronic inflammation and colitis-associated tumor growth via a PGE_2 signaling which mediates the crosstalk between tumor epithelial cells and macrophages. Our findings supports the notion that the existence of crosstalk between PPARδ and COX-2 signaling in CRC progression and may provide potential therapeutic targets for CRC prevention or treatment.

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EDUCATIONS/TRAINING

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RECENT PUBLICATIONS

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