

P055 Toll-like receptor-4 (TLR4) signaling is important for colitis-induced tumorigenesis: role of a disintegrin and metalloproteinase (ADAM)-17 and amphiregulin
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Background: Increased mucosal activation of ADAM-17, the TNF- α converting enzyme (TACE), has been reported in IBD. ADAM-17 release EGFR ligands and is associated with colorectal carcinogenesis. We have reported TLR4 signaling is linked to activation of EGFR in colitis.

Hypothesis: TLR4 regulates colorectal carcinogenesis through the ADAM-17-amphiregulin (AR)-EGFR signaling pathway.

Methods: **A human colorectal cancer cell line, SW480, was** stimulated with LPS. **Production of AR and expression and activation of ADAM-17** were analyzed by real-time PCR, ELISA and Western blot. Colitis-associated tumors were induced by IP injection of azoxymethane (7.4 mg/kg), followed by 2 cycles of 3% dextran sodium sulfate treatment for 7 days changing to water for 14 days thereafter. Inflammation and dysplasia were assessed histologically. ADAM-17, AR, and phosphorylated EGFR were examined by Western blot, real-time PCR and immunohistochemistry.

Results: LPS induced and activated ADAM-17 in SW480. LPS induced AR expression was blocked by ADAM-17 inhibitor TAPI-2 (10mM). In the mouse model, TLR4 deficiency led to a profound reduction in colorectal tumorigenesis and lower levels of AR in colonic tissues.

Conclusion: Our results suggest an important link between TLR4 signaling and inflammation associated colorectal carcinogenesis through EGFR.