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Extended Abstract

Childhood colitis aggravates gut barrier impairment via miR-196 when exposed to another episode of inflammation in adult-life

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Abstract

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Background & Aims: Mounting evidence suggests that adverse early-life events influence the perinatal programming and maturation of the immune system, predisposing the host to complex diseases including inflammatory bowel diseases (IBD). We hypothesized that neonatal colonic inflammation generates long range epigenetic memory that aggravates epithelial barrier impairment when exposed to another episode of inflammation in adult-life. Methods: Neonatal inflammation (NI) was induced by intra rectal administration of trinitrobenzene sulfonic acid (TNBS, 130 mg/kg) on postnatal day 10. Another dose of TNBS (80 mg/kg) was applied to induce adult inflammation (AI) six weeks after NI. All 4 groups of rats (Veh+Veh, NI+Veh, Veh+AI, and NI+AI) were euthanized 7 days later. Results: In NI+AI rats, we observed an aggravated epithelial damage, evidenced by exacerbated increase in colonic permeability, when compared with the other three groups of rats ($p<0.01$). We also tested the double-hit injury strategy in adult 6-week old rats given 130 mg/kg TNBS. After 6 weeks of remission, another episode of adult inflammation was induced with TNBS (AI+AI rats). There was no heightened tissue injury in AI+AI vs Veh+Veh, AI+Veh, and Veh+AI rats; noticeably less permeability was detected when compared to the NI model. Thus, aberrant epithelial damage occurs preferentially after colonic injury in the neonates. Molecular studies revealed a marginal decrease in Cdh1 mRNA and a significant reduction in E-cadherin protein in the colon mucosa of NI+AI rats, while Occludin, ZO-1, Claudin 1, Claudin 5, and Claudin 7 remained unchanged. To investigate the epigenetic mechanism underlying the loss of E-cadherin, we carried out miRNA arrays. miR-139, 196, 547, and 3596 were significantly upregulated whereas Let-7e, miR-19a, 96 and 101a were markedly repressed in NI+AI vs the other three groups of rats. Importantly, miR-196 is significantly elevated in patients with Crohn???s disease or colon cancer, indicating a

human clinical correlation. Bioinformatics analysis predicted E-cadherin, a key adhesion molecule involved in gut epithelial integrity, as a target of miR-196. To determine its role in regulating E-cadherin, we overexpressed miR-196 in HT29 colorectal cancer cells and found a significant decrease in E-cadherin mRNA and

protein ($p<0.01$). Thus, we postulated that a miR- 196 inhibitor might decrease NI-induced disease susceptibility and might ameliorate epithelial barrier injury in NI+AI rats. Intervention study with miR-196 inhibitor is currently ongoing. Conclusions: Severe neonatal colonic inflammation renders the host susceptible to aggravated epithelial damage in part by upregulating miR-196, which in turn downregulates E-cadherin, resulting in exacerbated increase in colonic permeability. miR-196 could serve as a therapeutic target in IBD and colitis-associated colon cancer.

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