

# Role of intestinal epithelial cells NF- $\kappa$ B in host response to ingestion of low doses of cadmium

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Chronic gastrointestinal inflammation is a great concern to human medicine, veterinary medicine, and food animal production. Minor disruptions to the homeostatic equilibrium of the intestinal tract can lead to Inflammatory Bowel Disease (IBD), Crohn's disease, and ulcerative colitis, which affect approximately 1.4 million people in the United States. Further, prolonged bouts of inflammation could similarly cause IBD in dogs and are contributing factors to colic in horses and depressed production of food animals. Low levels of cadmium are commonly found in water runoff and accumulation can occur in plants, seafood, and soft tissues of mammals. This heavy metal is now listed 7th in the priority list of hazardous substances and is believed to promote inflammation. This study explored the role of intestinal epithelial cells (IECs), and more specifically the canonical NF- $\kappa$ B pathway of these cells, in host mucosal responses to repeated ingestion of cadmium. Control wild-type C57BL/6 and IKK $\beta$  $\Delta$ IEC mice, which lack IKK $\beta$  in IECs, were maintained in conventional SPF housing (n=5 per group) and provided cadmium as CdCl<sub>2</sub> (10  $\mu$ M or 2 ppm) in drinking water for 14 days. Analysis of total sIgA in fecal samples collected on days 0, 7, and 14 showed that cadmium treatment reduces sIgA levels in both groups of mice. We also found that repeated ingestion of cadmium differentially affected the frequency of lymphocyte subsets in mesenteric lymph nodes (MLNs) of IKK $\beta$  $\Delta$ IEC and control wild-type mice and increased percentage of B cells while reducing the percentage of T cells in IKK $\beta$  $\Delta$ IEC mice. Furthermore, cadmium treatment enhanced gut TGF $\beta$  and TNF $\alpha$  mRNA responses to the bacterial product cholera toxin in IKK $\beta$  $\Delta$ IEC mice. Taken together, our data suggest that the canonical NF- $\kappa$ B in intestinal epithelial cells plays a key role in host response to environmental pollutants and subsequent inflammatory status in the gastrointestinal tract.