LOW DIETARY IRON INTAKE RESTRAINS THE INTESTINAL INFLAMMATORY RESPONSE AND PATHOLOGY OF ENTERIC INFECTION BY FOOD-BORNE BACTERIAL PATHOGENS

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Introduction and objectives
Orally administrated iron is suspected to increase susceptibility to enteric infections among children in infection endemic regions. We investigated the effect of dietary iron depletion and supplementation on the pathology and local immune responses in intestinal infection models.

Materials and Methods
6 Weeks old wild-type C57BL/6 mice were put on an iron-restricted (2-6 mg Fe/Kg), normal-iron diet (45 mg Fe/Kg), or high-iron diet (225 mg Fe/Kg) (n=5 per group). After 2 weeks the mice were orally challenged with Citrobacter rodentium. After another 2 weeks the gut microbiome was determined and inflammatory markers were assessed in plasma, tissue and faeces. Survival of Caenorhabditis elegans infected by Salmonella Typhimurium, pre-incubated with increasing iron concentrations, was tested (a simple gut infection model).

Results and discussion
Dietary intervention significantly altered tissue iron stores and microbiome analysis revealed profound iron- and infection-induced shifts. After iron deprivation Parabacteroides became dominant, while animals on the medium/high-iron containing diets had an Allobaculum dominated microbiota. Remarkably, fecal levels of the innate defensive molecules and markers of inflammation lipocalin-2 and calprotectin were not influenced by dietary iron intervention alone, but were markedly lower in mice on the iron-deficient diet after infection. Furthermore, mice on the iron-deficient diet tended to have a lower grade of colon pathology and to gain more weight. Complementary experiments showed that iron-deprivation was associated with prolonged survival of the nematode Caenorhabditis elegans after infection with Salmonella enterica serovar Typhimurium and, importantly, that iron increased the pathogenicity of this pathogen.

Together, these data show that iron limitation restricts disease pathology upon bacterial infection in two different animal models. However, our data also showed decreased intestinal inflammatory responses of mice fed on high-iron diets. Thus additionally, our study indicates that iron influences several processes at the intestinal host-pathogen interface and that the clinical outcome of oral iron administration is difficult to predict as this may highly depend on host iron status, immune status and the gut microbiota composition.

Theme: Model systems