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Author's response

We have shown that a diet that is deprived of iron prevents ileitis in a mouse model of Crohn's disease ($TNF^{deltaARE}$ mice).[1] In his comment, Buchman[2] was concerned that we misinterpreted our findings, as he supposed that sulphate may be more important than iron in the development of colitis in our rodent experiments. Most importantly, according to the composition of the experimental diets used in our studies (diet C1000 and C1038, Altromin GmbH, Lage, Germany), the total amount of sulphate salts (magnesium sulphate, iron sulphate, manganese sulphate and copper sulphate) in the control diet is comparable with the amount added to the low iron-sulphate diet (6586 vs 6520 mg/kg). The total sulphur content is 2792 and 2696 mg/kg, respectively. Thus, we can exclude that the observations we made arose from substantial differences in the content of sulphur-containing molecules in the diets. Moreover, besides in vivo feeding experiments, we could show in vitro that iron, given as ferric nitrilotriacetate (FeNTA), induces endoplasmic reticulum stress and apoptosis in the intestinal epithelial cell line Mode-K, which provides another piece of information speaking in favour of a direct role of luminal iron in inflammatory bowel diseases (IBD). Nevertheless, the issues addressed by Buchman about the influence of sulphate-reducing bacteria (SRB) and sulphide production in the intestine for the development and perpetuation of IBD are relevant to some extent. It is true that hydrogen sulphide has been reported to have toxic effects on intestinal epithelial physiology and that diets rich in sulphur-containing compounds have been associated with disease status. However, depending on the bioavailability and host susceptibility, it is important to note that hydrogen sulphide may not necessarily have detrimental effects.[3] As already stated in the original published version of our paper, mice fed a diet with a low content of iron were characterised by a decreased mean sequence occurrence of *Desulfovibrio* species in the caecum. All studies dealing with the implication of sulphide in IBD focused actually on ulcerative colitis or pouchitis, and no data have been published concerning Crohn's disease.[4 5] Since *Desulfovibrio* spp. are strictly anaerobic bacteria requiring a reduced environment to grow (<−100 mV), their occurrence in proximal parts of the intestine in $TNF^{deltaARE}$ mice, although unlikely, warrants further investigations, especially with respect to mucosa-associated communities. One explanation for the sensitivity of SRB towards depletion of iron in the gut lumen may be that important enzymes involved in the SRB metabolism contain iron in their active site, including hydrogenases of the [FeFe], [NiFe] and [NiFe(Se)] type. Also intestinal SRB such as *Desulfovibrio* spp. may benefit from a competitive advantage via Fe (III) reduction to gain energy when iron is provided in the diet. Nonetheless, it is also conceivable that SRB cause precipitation of Fe(II) as insoluble iron sulphide[6] or that iron is trapped in exopolymers produced by SRB,[7] showing that the influence of iron on the ecology of the SRB populations in the gut is still an open field of research. Altogether, we conclude that more work is needed to reach consensus regarding the role of SRB and sulphide in ileitis, but no matter what the outcome is, luminal iron can act independently. Feeding trials using different sources of iron should give definitive answers on the role of dietary iron in IBD.

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Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators

We read with interest the study by Sokol *et al* in *Gut*, emphasising the need for co-treatment with immunomodulators in patients receiving infliximab maintenance therapy. Concomitant use of immunosuppressives was associated with reduced disease activity and infliximab dose escalation, presumably through a lowered frequency of antibody formation.[1]

Although adalimumab is a 100% human anti-tumour necrosis factor monoclonal antibody, it is not devoid of immunogenicity. Antibodies against adalimumab have been reported in 2.6–38% of patients treated for Crohn's disease or rheumatoid arthritis.[2] However, the long-term efficacy of the combination of adalimumab plus immunosuppressives in this setting is not known. One observational study from Karmiris *et al* performed at a single tertiary care centre

Author's response

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Notes