Modulation of the inflammatory response by hydrogen sulfide in a model of colitis-associated cancer

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Chronic inflammation is now accepted as a key component of tumor progression and development (Hanahan and Weinberg, 2011) and inflammatory bowel diseases (IBDs) are considered major risk factors for colorectal cancer (Eaden et al., 2001). Several evidences link H_2S to colonic nociception, inflammatory bowel disease (IBD) and colorectal cancer. The exact mechanisms and pathways by which H_2S exerts its multitude of effects are not yet fully understood, but its involvement in physiological and pathophysiological conditions of the colon is becoming evident and several studies support the anti-inflammatory activity of H2S in experimental colitis (Xu et al., 2005; Fiorucci et al., 2007; Wallace et al., 2009).

The aim of the present study was to evaluate the role of H2S during the pathogenesis of colitis-associated cancer induced by infection with the intestinal bacteria Helicobacter hepaticus (Hh).

Infection of 129SvEvS6/Rag2-/- mice with Hh for three consecutive days led to the development of severe intestinal inflammation, characterized by marked epithelial cell hyperplasia, extensive inflammatory infiltrates and goblet cell depletion that is entirely dependent on innate immunity. Sustained inflammation in the colon of Hh-infected mice was correlated with a marked reduction (**P<0.01) of H2S synthesis at 3 and 6 weeks. Analysis of both protein and mRNA of H2S synthesizing enzymes cystathionine-beta-synthase (CBS) and cystathionine-gamma-lyase (CSE) was carried out on colon samples from healthy and Hh-infected mice at 6 weeks to evaluate the contribution of these enzymes in H2S production during Hh inducing colitis. The results demonstrated that both enzymes were constitutively expressed in the colon of healthy mice and that CBS, but not CSE, was significantly reduced during colitis development. Indeed, H2S synthesis by healthy and inflamed colon occurs mainly via CBS enzyme. Infact, when H2S synthesis was measured in colonic samples from healthy and infected mice in presence of the inhibitor of CBS (CHH, 3 mmol/L) or CSE (PAG; 10 mmol/L), we observed that CHH reduced H2S synthesis by ∼65% (***P < 0.001, vs control) in healthy mice and by ∼50% (°°P < 0.01, vs control) in Hh-infected mice, whereas the CSE inhibitor (PAG) had any effect. Finally, we found that enhancement of H2S levels in Hh-infected mice, obtained by administration of L-cysteine (1g/Kg) or diallyl trisulfide (DATS) (50mg/Kg), resulted in a significant reduction of inflammation in the distal part of the colon (*P<0.05). On the other hand, daily administration of CHH (10mg/Kg) to infected mice resulted in exacerbation of colitis (°°P < 0.01).

In conclusion, these results demonstrate that H2S has a protective role in Hh-induced colitis.

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