Targeting metallothionein in DSS-colitis points to new therapeutic strategies for IBD patients

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Introduction Inflammatory bowel diseases (IBD) are chronic intestinal inflammatory disorders. To date, the expression of metallothioneins (MTs), multifunctional acute stress proteins, in IBD patients and their role during intestinal inflammation is indistinct. Our aim was to address a functional role to the presence or absence of MTs during gut inflammation.

Materials and Methods Metallothionein knockout ($MT^{-/-}$), transgenic ($MT^{+/+}$) and wild type mice (WT) were subjected to 4% Dextran Sulfate Sodium (DSS) for 7 days followed by 7 days of normal drinking water. Body weight and mortality were recorded daily. Anti-MT antibody (or isotype control) treatment was used in a curative setting to study the effect of exogenous blocking of MTs during experimental colitis. Inflammatory response and serum zinc levels were assessed.

Results Mice lacking MT showed a significant higher survival rate compared to $MT^{+/+}$ mice ($p<0.05$; 90% survival for $MT^{-/-}$ mice versus 52% for $MT^{+/+}$ mice). During the recovery period, histological inflammation, neutrophil infiltration and epithelial proliferation were in favor of $MT^{-/-}$ mice ($p<0.05$). Baseline serum zinc levels were significantly lower in the $MT^{+/+}$ mice ($p<0.05$). Zinc levels decreased during the course of colitis in all three groups but this was less pronounced in the $MT^{-/-}$ mice. DSS exposed mice treated with the anti-MT antibody tended to lose less body weight and scored better for histological inflammation compared to control treated mice at day 10. Inflammatory cell infiltrate, represented as macrophages, was significantly lower in the anti-MT treated mice compared to control mice ($p<0.05$). Improved recovery of anti-MT treated mice was modulated by an enhanced hypoxic adaptive response with significant higher levels of the beneficial hypoxia-inducible factor 1 alpha and an increased vascularization compared to the control group ($p<0.05$).

Conclusion A low MT profile during colitis was associated with enhanced recovery and prolonged survival of DSS-induced colitis. Targeting extracellular metallothioneins using anti-MT antibody confirmed the beneficial properties of a low MT profile during recovery of colitis and allows extrapolation to future therapeutic opportunities for patients suffering from IBD.