Hyposulfataemia and gastrointestinal physiology

P.A. Dawson,[1] N. Strachan,[1] S. Huxley,[1] M.A. McGuckin[2] and D. Markovich,[1] [1]School of Biomedical Sciences, University of Queensland, St Lucia, QLD 4072, Australia and [2]Mater Medical Research Institute, Mater Hospital, South Brisbane, QLD 4101, Australia.

The NaS1 sulfate transporter is essential for maintaining serum sulfate concentrations. Two polymorphisms (SNPs) exist in the coding region of the human NaS1 gene: R12X and N174S. We have generated a Nas1 null (Nas1-/-) mouse, which exhibits hyposulfataemia. Furthermore, Nas1-/- mice have a decreased sulfate content of intestinal mucins, which are the major macromolecular component of gastrointestinal (GI) mucus and the mucosal glycocalyx that lubricates and protects the underlying epithelium. This is of particular relevance to GI physiology because sulfate is proposed to play an important role in protecting mucins from degradation. The aims of this study were to functionally characterise the human NaS1 SNPs (R12X and N174S) and to determine the consequences of hyposulfataemia on GI physiology. Compared to wild-type NaS1, R12X and N174S led to a 100% and 60% loss of sulfate transport in *Xenopus* oocytes, respectively. Nas1-/- and Nas1+/+ mice were challenged orally with *C. jejuni* bacteria, or dextran sodium sulfate (DSS), an accepted model for inducing intestinal inflammation (colitis). *C. jejuni* colonised the stomach and intestines of both Nas1-/- (n=16) and Nas1+/+ (n=16) mice. Only 1 Nas1+/+ mouse developed systemic infection, whilst 9 of the Nas1-/- mice showed colonisation of systemic organs, including the liver. In an acute murine colitis model, DSS treatment (2.5% DSS in drinking water for 7 days) led to shorter intestines (P=0.006) in Nas1-/- mice (n=8), when compared with Nas1+/+ (n=7) mice, suggesting that hyposulfataemia leads to enhanced DSS-induced colitis. In conclusion, two loss of function SNPs exist in human NaS1 and Nas1-/- mice have a decreased defence from mucosal bacterial infection, and are more susceptible to DSS-induced colitis. These findings underline the importance of sulfated mucins in intestinal barrier function, and prompt studies of gastrointestinal mucins in humans with loss-of-function NaS1 polymorphisms.