

Physiological Interactions Between *Oxalobacter* and the Transporting Mucosa

Marguerite Hatch and Robert W. Freel

Department of Pathology, University of Florida, Gainesville, FL

Considerable evidence has emerged from both human and animal studies suggesting that *Oxalobacter* plays an important role in degrading dietary sources of oxalate (Ox^{2-}) in the intestine leading to reduced intestinal Ox^{2-} absorption and, consequently, lower urinary Ox^{2-} . A number of years ago, we proposed that, in addition to (passively) degrading dietary sources of Ox^{2-} , *Oxalobacter* may be able to derive Ox^{2-} from systemic sources by initiating or enhancing active secretion of endogenously derived Ox^{2-} . Subsequently, using various approaches, we were able to demonstrate that *Oxalobacter* can modulate intestinal Ox^{2-} transport by inducing colonic Ox^{2-} excretion. A beneficial consequence of this bacterial-enterocyte interaction is a significant reduction in urinary Ox^{2-} excretion due to this enteric Ox^{2-} shunt. The first approach involved comparing colonic handling of Ox^{2-} in rats that were colonized with *Oxalobacter* and rats that were not colonized. Colonization resulted in a complete reversal in the direction of net Ox^{2-} transport—from absorption in the non-colonized animals to secretion in the naturally colonized animal. Importantly, this change in intestinal handling was accompanied by a concomitant and significant reduction in urinary Ox^{2-} excretion. In the next approach, three groups of colonized rats were placed on different treatment regimens, including Ox^{2-} -supplemented food; ethylene glycol in the drinking water (as a source of endogenously derived Ox^{2-}) with no Ox^{2-} added to the food; and Ox^{2-} supplemented food with ethylene glycol treated drinking water. All rats exhibited Ox^{2-} secretion across the distal colon and, importantly, all rats remained colonized, including the group receiving ethylene glycol only. The results of the latter study are particularly significant because it was the first study to demonstrate that endogenously derived Ox^{2-} can sustain *Oxalobacter* colonization. Encouraged by these earlier observations, we sought to determine whether *Oxalobacter* colonization of a mouse model of Primary Hyperoxaluria Type 1 (PH1) could enhance enteric Ox^{2-} secretion and effectively reduce the hyperoxaluria associated with this genetic disease. Mice deficient in alanine-glyoxylate aminotransferase (AGT) with pure C57BL/6 backgrounds that develop hyperoxaluria were used in these studies. For comparison purposes, we also examined Ox^{2-} transport and urinary Ox^{2-} excretion in colonized C57BL/6 wild-type mice. In general, the results of these studies confirm that *Oxalobacter* colonization is consistently associated with a reduction in urinary Ox^{2-} excretion and changes in intestinal Ox^{2-} handling. In the colonized PH1 mouse model, urinary Ox^{2-} excretion was reduced 50 percent to within the normal range for C57BL/6 mice. Colonization of C57BL/6 mice was also associated with marked reductions in urinary Ox^{2-} excretion. Further, it was apparent that the caecum and distal colon contribute significantly to enteric Ox^{2-} excretion in colonized mice, whereas the proximal colon was involved to a lesser extent. Whether *Oxalobacter* can therapeutically reduce urinary Ox^{2-} excretion and influence stone disease or the progression of PH warrants long-term studies in a variety of patient populations.

Support: This work was supported by the Oxalosis & Hyperoxaluria Foundation and NIDDK.
