

Title: Therapeutic Potential of *Oxalobacter formigenes*-derived Bioactive Factors for Hyperoxaluria, Hyperoxalemia, and related Kidney Stones

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Hyperoxaluria is a major risk factor for kidney stones and it has no specific therapy. *Oxalobacter formigenes* (*Of*) colonization is associated with reduced stone risk. *Of* interacts with colonic epithelium and induces colonic oxalate secretion and reduced urinary oxalate excretion via an unknown secretagogue. The difficulties in sustaining *Of* colonization underscore the need to identify the *Of*-derived factors inducing colonic oxalate secretion. We therefore evaluated the effects of *Of* culture conditioned medium (CM) on apical ^{14}C-oxalate uptake by human intestinal Caco2-BBE (C2) cells. Compared with control medium, *Of* CM significantly stimulated oxalate uptake (>2.4-fold), whereas CM from *Lactobacillus acidophilus* did not. Treating the CM with heat or pepsin completely abolished its bioactivity, and selective ultrafiltration reveals that the factors have molecular masses between 10-30 kDa. Treatment with the protein kinase A inhibitor H89 or the anion exchange inhibitor DIDS completely blocked the CM-induced oxalate transport. Knockdown of the oxalate transporter SLC26A6 also significantly reduced the induction of oxalate transport by CM. In a mouse model of primary hyperoxaluria type 1, rectal administration of *Of* CM significantly reduced (>32.5%) urinary oxalate excretion and stimulated (>42%) distal colonic oxalate secretion. We conclude that *Of*-derived bioactive factors stimulate oxalate transport in intestinal cells through mechanisms including PKA activation. The reduction in urinary oxalate excretion in hyperoxaluric mice treated with *Of* CM reflects the *in vivo* retention of biologic activity and the therapeutic potential of these factors. Importantly, we had already made a significant progress towards characterization of these factors given their remarkable potential to serve as novel therapeutic agents for prevention and/or treatment of hyperoxaluria, hyperoxalemia, and related kidney stones

Biography

Dr. Hassan obtained his MD from University of Khartoum Medical School (Sudan) in 1994, and his PhD in Investigative Medicine from Yale University School of Medicine in 2007. He is currently serving as a physician-scientist at the level of an assistant professor in the section of Nephrology, department of Medicine, The University of Chicago. He has published more than 11 papers in reputed journals and his research is funded by the National Institue of Health (NIH).

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