STONES

New pathway to prevention of L-cystine stones

Crystal growth inhibitors could be a novel treatment for patients with L-cystine kidney stones, according to a recent study published in *Science*.

Although rare—affecting only around 20,000 patients in the USA—cystine stones tend to be larger than the more common calcium oxalate stones, and are more likely to recur. The main treatment for cystine stones is thiols, which react with L-cystine to produce more soluble disulfides. However, these drugs have a plethora of adverse effects, and are often ineffective at non-toxic doses. A group led by Michael Ward at New York University, NY, USA, has investigated the effect of crystallization inhibitors on L-cystine crystals *in vitro*, with a view to developing more benign treatments.

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“Our goal was to devise an approach to block the growth of L-cystine crystals, which of course must be one of the critical stages in L-cystine stone formation” explains Ward. “Moreover, we wanted to devise a treatment ... without the side effects of the current suite of thiol drugs”.

Ward and colleagues used real-time *in situ* atomic force microscopy (AFM) and parallel bulk crystallization studies

to determine the effects of tailored crystal growth inhibitors, including the molecule L-CDME, on growth of L-cystine crystals under near-physiological conditions *in vitro*.

During growth, AFM reveals that L-cystine crystals exhibit hexagonal hillocks that expand in a spiral pattern. L-CDME—which contains methylester groups in place of the carboxylate groups in L-cystine—acts as a structural mimic of L-cystine, causing roughening of the otherwise linear crystal step edges, rounding of the hillock corners and reduction in the step velocity, all of which were reversible once L-CDME was removed from the crystal growth medium.

L-CDME also slowed crystal growth, an effect mirrored by a change in the crystal habit from plates to small hexagonal needles. When treated with L-CDME, the area of the crystal face was reduced by a factor of 1,000—thus the resulting crystals were 1,000 times smaller. The effects were dose-dependent, with total crystallization yields decreasing with increasing L-CDME concentration, and almost complete inhibition at 2 mg/l.

These changes may affect not only crystal aggregation, but also the attachment of L-cystine crystals to renal cells—another step in the formation of stones. The concentration of L-CDME required to exert these effects is well below

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the level thought to be toxic to cells *in vitro* and to rats.

These data suggest that L-CDME is a viable potential agent for prevention of L-cystine kidney stones. Mouse studies are currently underway. If successful, they could lead to development of a much needed treatment for this rare but serious disease.

Annette Fenner

Original article Rimer, J. D. et al. Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design. *Science* 330, 337–341 (2010)