Flies reveal kidney stones in-the-making

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Kidney stones usually make their presence known suddenly, often sending a person to the hospital in excruciating pain. Each year in the U.S. more than a million people seek medical attention for kidney stones, technically called nephrolithiasis. The total annual cost of treatment exceeds $2.1 billion, according to the National Kidney and Urologic Diseases Information Clearinghouse.

Although kidney stone pain may seem to come out of nowhere, the hard collections of minerals that block kidney tubules and ureters originate and grow over weeks or months. Learning more about how they form can suggest ways to detect them at earlier stages, prevent recurrence following lithotripsy (shock waves that break up the stone) or surgery, and possibly prevent them altogether if susceptible individuals can be identified.

Experiments using the fruit fly *Drosophila melanogaster* not only provide a glimpse of kidney stone formation over a fly's short lifetime, but have identified an important role zinc plays in the disease process in flies and in people. Thomas Chi, MD, Clinical Instructor and Endourology and Laparoscopy Fellow in the Department of Urology at the University of California, San Francisco, will discuss these experiments today at the Genetics Society of America's 54th Annual *Drosophila* Research Conference in Washington D.C., April 3-7, 2013.

"There's been little to no change in medical treatment for urinary stones in the last 20 years. While surgical (which includes lithotripsy) treatments have advanced at a rapid pace, our ability to prevent kidney stones or their recurrence is extremely limited," said Dr. Chi.

In flies genetically predisposed to develop stones, researchers can track the origins of the condition, and can also screen drugs, medical therapies, and other genes that counter stone formation. The insects develop pebble-like masses of phosphorus and calcium that look like tiny human kidney stones. The growths lodge in the fly's Malpighian tubule, which is the equivalent of the convoluted tubules in the million or so microscopic nephrons that make up a human kidney.

Kidney stone formation is an example of "ectopic calcification," in which calcium hydroxyapatite, a normal constituent of bones and teeth, forms elsewhere. Understanding how kidney stones form may also shed light on other sites of ectopic calcification, such as the coronary arteries.

In many animal models of kidney stones, researchers feed toxins such as antifreeze – ethylene glycol – to induce the condition. Obviously, this is not how the human condition begins. However, fruit flies with a mutation in the gene that encodes the enzyme xanthine dehydrogenase develop kidney stones that are remarkably like their human counterparts, rich in calcium hydroxyapatite.

Dr. Chi and his colleagues used the fly model to look for genes which, when silenced, prevent or ameliorate kidney stones. The researchers scrutinized over 80 genes, based on known functions, and narrowed them down to fewer than 10 that are involved with formation of kidney stones. Genes related to zinc transport in particular seemed to play a major role, demonstrating the importance of the element in stone formation.

The researchers developed a visually striking method to watch fly kidney stones form. They labeled calcium hydroxyapatite with fluorescent bisphosphonate, an osteoporosis drug. The technique reveals tiny green glowing balls that are the seeds of kidney stones.

Dr. Chi calls the beginnings of the stones "calcified nanoparticles" and puts their size into perspective. "If you had a rope from Hong Kong to San Francisco, to find a calcified nanoparticle, you'd be looking for a 5 to 10 foot segment on that rope." The nanoparticles in the fly may be an early equivalent of precursor lesions in people called Randall plaques, he added.

Zinc transport is important to nanoparticle formation. "Zinc is present throughout the body, and is very important for a number of physiologic processes. We are NOT saying that making the whole body zinc deficient could be an effective approach to treating kidney stones. But if we could somehow control the microenvironmental zinc levels at the key stage in stone development, that approach might offer us an effective new therapy," Dr. Chi explained.

The researchers hope that their findings will lead to new options for kidney stones. "If we can get to them before they form, we'd cut way back on the number of people needing surgery every year, which is our goal," Dr. Chi said.

Provided by Genetics Society of America

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