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Kidney News

April 2016 | Vol. 8, Number 4

Empathy and Communication are Critical Skills that Can Improve Care

By Eric Seaborg

During her nephrology fellowship, Jane Schell, MD, was surprised at how unprepared she felt to talk with elderly and very ill patients about their poor prognoses and the probably disturbing trajectory of their diseases.

Her personal discomfort led her into a research project where she discovered that her sense of a lack of preparedness—leading to a hesitancy to engage—was widely shared even among her older, established colleagues. And patients reported that this failure of communication left them feeling uncertain, confused, and not ready for the challenges they faced.

A regular part of nephrology practice is delivering emotional news and guiding patients as they deal with life-and-death topics like dialysis initiation and withdrawal. Yet nephrologists do not receive education in skills—communication and empathy—that should be considered as important as other aspects of their training, according to Schell, who is now a practicing nephrologist and palliative care physician at the University of Pittsburgh.

"Most physicians are not adequately prepared to have these kinds of conversations with seriously ill patients," said James A. Tulsky, MD, chair of the department of psychosocial oncology and palliative care at the Dana-Farber Cancer Institute and a pioneer researcher in clinical empathy and communication. "There is very little in any of their training—whether it is medical school residency or fellowship—that focuses on communication skills in these difficult situations."

Patient outcomes: for better or worse

This training absence spans most specialties, despite strong evidence that physician empathy and communication improve patient care. A Joint Commission on Accreditation of Healthcare Organizations report found that communication failures were a root cause of more than 70 percent of serious adverse health outcomes in hospitals.

And conversely, studies show a clear association of clinical empathy with better patient outcomes. In two studies of

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Research on Crystal-Induced Cell Death Could Pave Way for New Molecular Targets for Treating Kidney Diseases

By Timothy O'Brien

Crystals play a role in the development and progression of a wide range of diverse diseases, from gout to atherosclerosis to kidney disease. New experimental findings suggest that these crystallopathies may involve a "regulated process" of crystal-induced cell death called necroptosis, according to a report in *Nature Communications*.

The study also clarifies the steps in the pathway leading to necroptosis, suggesting promising new therapeutic targets to limit crystal-induced cytotoxicity and tissue injury. Necroptosis is just one of several recently recognized categories of "necroinflammation"—with distinct molecular pathways—potentially relevant to a wide range of kidney diseases.

Led by Prof. Hans-Joachim Anders of Ludwig-Maximilians-Universitat in Munich, the researchers performed a series of experiments to understand the types and mechanisms of cell death in crystal-induced tissue injury. Various crystallopathies share common features, suggesting a similar underlying pathogenesis. Crystal-induced inflammation has been considered the main mechanism by which cell death occurs.

But recent studies have identified new pathways of "regulated necrosis"—in which cell death results from active processes leading to cell necrosis that, in turn,

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Cell Death

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promotes inflammation. In their experiments, Prof. Anders and colleagues focused on the pathway of necroptosis: a regulated process of necrotic cell death specifically dependent on receptor-interacting serine-threonine kinase 3 (RIPK3) and mixed lineage kinase domain-like (MLKL).

The investigators exposed in vitro kidney epithelial cells to four types of crystals involved in human crystallopathies: calcium oxalate (CaOx), monosodium urate, calcium pyrophosphate dihydrate, and cystine. Under all conditions, cells died by primary necrosis. Flow cytometry showed that CaOx-induced cell death occurred without signs of apoptosis involving caspases.

Rather, all four types of crystals induced proteins involved in the necroptosis pathway: RIPK1, RIPK3, MLKL, and tumor-necrosis factor receptor 1 (TNFR1). Furthermore, crystal-induced cell death was at least partially prevented by exposure to necrostatin-1, a RIPK1 stabilizer. In cells exposed to CaOx crystals, necrostatin-1 completely prevented crystal-induced death.

Further studies were performed in a mouse model of crystal nephropathy, in which oxalate exposure leads to crystal-induced tissue injury and organ failure. Oxalate induced CaOx deposits in *Ripk3*- and *Mlkl*-deficient mice, as in wild-type animals. However, all functional and structural indicators of crystal nephropathy were significantly reduced in the *Ripk3*- and *Mlkl*-deficient mice—including serum creatinine levels, markers of tubule necrosis, and neutrophil recruitment.

Additional experiments suggested that necroptosis is responsible for inducing inflammation in the presence of crystal nephropathy, as inhibiting necroptosis also prevented inflammation. There was also evidence of secondary necroptosis driven by TNF.

The findings add to a growing body of evidence on the bidirectional causal associations between kidney injury and inflammation. Prof. Anders is also coauthor of a recent review in the *Journal of the American Society of Nephrology* that highlights the growing body of evidence for a "genetically determined and regulated process" of necroinflammation. (Co-authors of the *JASN* review are Drs. Shrikant R. Mulay of Klinikum der Universität München and Andreas Linkermann of Christian-Albrechts-University Kiel.)

The concept of necroinflammation provides a unifying theory of the relationship between kidney injury and inflammation, which are "reciprocally enhanced in an autoamplification loop," according to the *Nature Communications* study. Just in the last few years, researchers have made progress toward outlining a number of different molecular pathways by which necrosis induces inflammation and inflammation induces necrosis.

By showing that crystal-induced cell death occurs through a regulated process and identifying the mediators involved in necroptosis, the new study identifies some potentially effective new therapeutic targets. In vivo experiments showed reduced evidence of crystal nephropathy in animals treated with necrostatin-1; as well as etanercept, which blocks TNF-α; and R-7050, a TNFR internalization inhibitor.

What's the relevance to human kidney disease? On review of a large series of human kidney biopsies, Anders and colleagues found CaOx crystals in association with acute tubular injury in 10% of 4125 cases of acute kidney injury. On immunostaining, crystal-induced cytotoxicity in human cells appeared similar to that in mouse cells, including activation of MLKL.

Alberto Ortiz, MD, PhD, of Fundacion Jimenez Diaz and University Autonoma of Madrid noted, "Indeed, oxalate may cause acute kidney injury in 'juicers'—individuals who may inadvertently consume huge amounts of oxalate-rich fruit and vegetables by juicing these in the course of 'healthy' dieting."

The results may help to refine understanding of the process leading to crystal-induced cell death in several human diseases. "Cell death in this context has hitherto been regarded mainly as a passive process of cell loss due to irreparable damage," Anders said. "But we have now demonstrated that it is the outcome of a regulated process, which actively eliminates cells."

Treatments focusing on specific mediators of the necroptosis pathway could offer important advantages, compared to previous strategies directed at the inflammatory reaction. If blocking those mediators can prevent crystal-induced cell death, it might also impede the development of chronic inflammation—with potentially important implications for management not only of acute kidney injury, but also other conditions such as gout and atherosclerosis. Prof. Anders and colleagues write, "Together, TNF-α/TNFR1, RIPK1, RIPK3, and MLKL are molecular targets to limit crystal-induced cytotoxicity, tissue injury, and organ failure."

In addition to necroptosis, the *JASN* review describes five additional pathways of necroinflammation: ferroptosis, mitochondrial-permeability transition-medicated regulated necrosis, pyroptosis, "NETosis" involving neutral extracellular traps, and mitotic catastrophe. These regulated processes of necroinflammation could contribute to a wide range of other important kidney diseases, such as sepsis/urosepsis, acute tubular necrosis, rapidly progressive glomerulonephritis, and thrombotic microangiography.

Together, all of these processes suggest an extensive list of molecular therapeutic targets with the potential to interrupt the process of necroinflammation. A key issue will be whether delayed treatment aimed at inhibiting these regulated processes of cell death will be able to prevent kidney injury in AKI and other conditions. Mulay, Linkermann, and Anders concluded, "The various aspects of necroinflammation offer great opportunities for novel discoveries and eventually also for novel treatment options for patients with kidney disease."

"The impact of an improved understanding of the molecular drivers of regulated necrosis and subsequent inflammation may extend well beyond the kidneys," Ortiz said. He pointed out several systemic diseases in which crystals play an essential role in pathogenesis, and which may be amenable to new treatment approaches targeting regulated necrosis and inflammation: "These include oxalate crystal deposition, which is systemic in oxalosis; atheroembolism, which consists of systemic cholesterol crystal emboli and currently has no specific therapy; and cystinosis, a systemic disease in which cysteamine therapy delays but may not completely prevent systemic complications."

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Online ASN Communities Expand Member Communication Options

By Zach Cahill

During the past five years, the American Society of Nephrology has seen significant membership growth. ASN now represents a more complete picture of the nephrology community, including a significant international presence and health professionals across many job roles and interest areas. To engage with this diverse membership, ASN has established a new member benefit: ASN Communities.

ASN Communities provide an online platform for discussion, networking, and collaboration among nephrologists around the world. Unveiled in March 2016, the Communities allow members to connect to each other, to the society, and to the broader kidney community. Every ASN member has access to the ASN Communities and may log in through the ASN website with the same username and password they already use.

By providing many options for engaging with colleagues, the Communities are designed to fit the busy lifestyle of ASN members. Daily digest emails summarize the latest conversations, allowing members to keep up with discussions on their own time. Members may respond to or begin a new thread via email from any device. The site also includes a resource library, allowing members to share presentations, documents, videos, and more. The site even recommends contacts based on individual interests, institution, or geographical area.

For the past two months, the society has tested the site with a small group of members in an effort to create an easy-to-use and valuable platform. During that time, members have used the Communities to get advice on issues they face in daily practice, to share ideas on addressing nephrology workforce issues, and to provide input to the society on public policy matters. Kidney professionals from around the world—including Bahrain, China, India and Italy—have all engaged with ASN Communities, interacting with professionals at all levels, from nephrology fellows to "seasoned" nephrologists. ASN members engaged in the Communities represent all the different facets of nephrology: PhD basic researchers, academics, practicing nephrologists, and many more.

As engagement grows, the Communities will become a venue for topical debates, "Ask the Expert" opportunities, and journal article discussions. Over the coming months, ASN plans to introduce interest-based communities, which will serve as a virtual home for members interested in in-depth discussions about a specific subject area with like-minded peers. Every member interested in a subject area will be able to join the group and be a part of exciting, relevant discussions led by engaged and respected Community leaders. Once established, each community will be able to have a voice in selecting its own leadership. The ASN Communities will also streamline member input on important topics, such as integrated care delivery models, maintenance of certification, and educational interests. The Communities will ensure ASN activities and priorities accurately reflect the vast interests of the society's growing membership.

To explore the new ASN Communities site, visit community.asn-online.org and join the conversation.

Zach Cahill is ASN Communities Associate.