Journal club

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Kidney stone disease affects about 12% of men and 5% of women during their lifetimes in the United States.

Intrarenal nephrocalcinosis is often asymptomatic, but can lead to significant kidney injury and renal failure.

Histopathology of human CaOx nephropathy and microarray analysis of rodent CaOx nephropathy shows a substantial contribution of interstitial inflammation to tissue remodeling.

Inflammation and tissue remodeling in various crystallopathies involve a unique intracellular signaling pathway for the secretion of the proinflammatory cytokine IL-1β: the NLRP3 inflammasome/ apoptosis-associated speck-like protein containing CARD/ caspase-1 (NLRP3/ASC/caspase-1) axis.
Innate immunity has been viewed as the first line of defense discriminating “self” from “nonself”.

Innate immunity serves as a sophisticated system for sensing signals of “danger,” while remaining unresponsive to nondangerous motifs.

Such a model allows for coordinate activation of immune system antimicrobial and tissue repair functions in response to infection or injury, while avoiding collateral damage in situations in which harmless nonself is present.
The NOD-like receptors (NLRs) are a set of intracellular pattern-recognition receptors (PRR) that recognize pathogen-associated molecular patterns (PAMPs), as well as host-derived danger signals (danger associated molecular patterns, DAMPs).

NLR assemble into high-molecular weight, caspase-1-activating platforms called “inflammasomes”.

Inflammasomes control maturation and secretion of interleukins such as IL-1β and IL-18.
The NLR family is characterized by the presence of a central nucleotide-binding and oligomerization (NACHT) domain, which is commonly flanked by C-terminal leucine-rich repeats (LRRs) and N-terminal caspase recruitment (CARD) or pyrin (PYD) domains.

LRRs function in ligand sensing and autoregulation

CARD and PYD domains mediate homotypic protein-protein interactions for downstream signaling.

The NACHT domain, enables activation of the signaling complex via ATP-dependent oligomerization.

Members of the NLR family are generally considered to perform cytoplasmic surveillance for PAMPs or DAMPs.

Benko S, Philpott DJ, Girardin SE., Cytokine. 2008 Sep;43(3):368-73.
Caspases

- Caspases are cysteine proteases that initiate or execute cellular programs, leading to inflammation or cell death.

- They are synthesized as inactive zymogens, and their potent cellular activities are tightly controlled by proteolytic activation.

- Caspases are categorized as either proinflammatory or proapoptotic, depending upon their participation in these cellular programs.

IL-1β

• IL-1β is an important proinflammatory mediator that is generated at sites of injury or immunological challenge to coordinate programs as diverse as cellular recruitment to a site of infection or injury and the regulation of sleep, appetite, and body temperature.

• IL-1b activity is rigorously controlled by expression, maturation, and secretion; proinflammatory stimuli induce expression of the inactive IL-1β proform, but cytokine maturation and release are controlled by inflammasomes.

• An endogenous IL-1 receptor antagonist (IL-1RA) also regulates IL-1β action.
The NLRP3 inflammasome consists of the NLRP3 scaffold, the ASC (PYCARD) adaptor, and caspase-1.

A number of host-derived molecules indicative of injury activate the NLRP3 inflammasome:
- extracellular ATP
- Hyaluronan
- Fibrillar amyloid-b peptide

The NLRP3 inflammasome detects signs of metabolic stress:
- High extracellular glucose
- monosodium urate (MSU) crystals
- Uric acid

The NLRP3 inflammasome drives inflammation in response to a number of environmental irritants:
- Silica
- Asbestos
- UVB irradiation
- skin irritants such as trinitrophenylchloride, trinitrochlorobenzene, and dinitrofluorobenzene.
Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion

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Hypothesis

- CaOx crystals have an agonistic potential on NLRP3 and trigger IL-1β secretion.

- This process contributes to CaOx-induced tissue inflammation, for example, in nephrocalcinosis and/or CaOx nephropathy.
CaOx crystals activate DCs to secrete mature IL-1β.
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Mechanisms of CaOx crystal–induced IL-1β secretion.
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CaOx nephropathy in C57BL/6 mice.
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Role of MyD88, IL-1R, and IL-18 in CaOx nephropathy
Role of NLRP3, ASC, and caspase-1 in CaOx nephropathy.
Role of NLRP3, ASC, and caspase-1 in CaOx nephropathy.
Role of DCs in CaOx nephropathy
Role of DCs in CaOx nephropathy
Apyrase treatment in CaOx nephropathy in C57BL/6 mice.
Anakinra treatment in CaOx nephropathy in C57BL/6 mice.
Conclusion

- The present study is the first to demonstrate that AKI in crystal nephropathy largely depends on the capacity of intrarenal mononuclear phagocytes to trigger renal inflammation upon crystal recognition.

- NLRP3 inflammasome — an intracellular pattern recognition platform that translates danger signaling into secretion of mature IL-1β — is involved in the pathogenesis of CaOx nephrocalcinosis.

- CaOx-induced intrarenal IL-1β secretion originates from the intrarenal network of interstitial mononuclear phagocytes, which includes several DC populations.

- CaOx crystals also formed in the interstitial compartment, are internalized by interstitial cells.

- In vitro, phagocytic uptake was required for CaOx-induced IL-1β secretion in DCs. Potassium efflux from the cell, occurring upon cell membrane disruption or pore formation by bacterial toxins, is another trigger of NLRP3 activation in DCs. This is consistent with the mode of NLRP3 activation by other crystals.
Conclusions

- CaOx crystals did not trigger mature IL-1β secretion in TECs. However, TECs internalize CaOx crystals, inducing oxidative stress and tubular cell necrosis.

- Necrotic tubular cells release ATP, a potent NLRP3 agonist.

- There was a therapeutic effect of the recombinant IL-1 receptor antagonist anakinra in CaOx nephropathy in mice, which suggests that IL-1 blockade may also reduce renal inflammation and kidney damage in other crystal nephropathies.
Thank you