frontiers in Immunology

EDITORIAL
published: 01 November 2021
doi: 10.3389/fimmu.2021.795559

Editorial: Immunity and Inflammatory Response in Kidney Stone Disease

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Keywords: calcium oxalate, immunomodulation, inflammation, macrophage, microbiota, monocyte, nephrolithiasis, senescence

Editorial on the Research Topic

Immunity and Inflammatory Response in Kidney Stone Disease

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Edited and reviewed by:
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Specialty section:
This article was submitted to Molecular Innate Immunity, a section of the journal Frontiers in Immunology

Received: *15 October 2021*
Accepted: *19 October 2021*
Published: *01 November 2021*

Citation:
Thongboonkerd V, Yasui T and Khan SR (2021) Editorial: Immunity and Inflammatory Response in Kidney Stone Disease. Front. Immunol. 12:795559. doi: 10.3389/fimmu.2021.795559

Kidney stone disease (or nephrolithiasis) is a common urological disorder causing significant morbidity and financial burden in both genders at all ages around the globe (1). Its prevalence is increasing universally at an alarming rate (2–5). Moreover, the stone formation can trigger other renal and vascular disorders such as hypertension, chronic kidney disease and end stage renal disease (6–8). Kidney stones are mineral deposits mostly in the pelvis, free or attached to the renal papillae (9). Calcium oxalate (CaOx) is the main component of approximately 80% of all kidney stones, majority of them being idiopathic (10). Most of the idiopathic CaOx stones develop by attachment to sub-epithelial deposits of calcium phosphate on renal papillary surface, called Randall's plaques (RPs) (11, 12). Some of the stones form as an overgrowth on crystalline deposits within the terminal collecting ducts of the kidney (13). Both pathogenic mechanisms require periodic urinary supersaturation with respect to CaOx (i.e., hypercalciuria and hyperoxaluria) in association with low levels of its inhibitors (e.g., citrate and other urinary macromolecular inhibitors) (13, 14).

Results of clinical and experimental studies indicate increased expression of genes related to inflammation, immunity and complement activation pathways in renal tissue of experimental animals and stone patients (11). Inflammatory pathways are activated in human renal tissue around the RPs (15). Macrophages appear to be critically involved. M1-related genes are associated with promotion of stone formation, while M2-related genes are related to the stone suppression (16, 17). CaOx crystals induce polarization of M1 macrophages and stimulate inflammatory response in monocytes (18). On the other hand, M2 macrophages can phagocytose and degrade CaOx crystalline fragments (16–18). Macrophage differentiation is also influenced by androgen receptor, which regulates macrophage colony stimulating factor, a cytokine that polarizes monocytes and naïve macrophages into anti-inflammatory macrophages (19).

High oxalate can impact mitochondria of circulating monocytes, leading to altered macrophage polarization (promoting M1 over M2) (20). Immune dysfunction in stone patients may induce oxalate and CaOx-mediated overproduction of reactive oxygen species (ROS) within monocytes, damaging their mitochondria and impairing stone crystal clearance (16–18, 20). Exposure of the naïve bone marrow-derived macrophages to CaOx decreases expression of NAD-dependent protein deacetylase sirtuin-3 and increases proinflammatory mediators (17). In addition to oxidative stress, high oxalate and CaOx crystals can induce inflammatory response through the activation of NLR

family pyrin domain containing 3 (NLRP3) inflammasome, which triggers the release of proinflammatory cytokines IL-1B and IL-18 (21, 22). Inactivating NLRP3 may prevent oxalate damage by altering macrophage polarization. Antioxidant treatment of experimentally induced hyperoxaluria in rats also reduces the inflammatory responses and production of the inflammatory mediators (23, 24).

Indeed, inflammation in kidney stone disease can be the upstream (as a pathogenic factor) or downstream event (as a complication). Despite the aforementioned knowledge, the immunity and immune response in kidney stone disease remained unclear (mainly because they were under-investigated) and thus need further elucidations. This Research Topic therefore provides a great opportunity to highlight and promote research in this area. It is a concise collection of most recent basic, preclinical and clinical studies of immune mechanisms and immunomodulation of kidney stone disease.

A systematic review by Taguchi et al. provides an up-to-date knowledge on roles of macrophages in CaOx kidney stone formation. The article summarizes all the findings related to *in vitro*, *ex vivo* and *in vivo* functions of monocytes and all types of macrophages, including non-polarized and polarized ones, in CaOx kidney stone disease.

A research by Ma et al. shows that among C57BL/6N (B6N), 129, B6J and Balb/c mice, high-oxalate diet causes CaOx crystal deposits, increased renal uromodulin expression, renal inflammation and fibrosis only in the B6N mice. Backcrossing the 129 strain with B6N causes CaOx crystal deposits similar to the B6N mice, whereas co-housing study of microbiota adaptation seems to have no effects on CaOx crystal deposits. The authors conclude that genetic background, not microbiota, plays roles in strain-specific hyperoxaluria-induced kidney stone formation.

Another study by Chuenwisad et al. demonstrates that oxalate, CaOx monohydrate and urine from the stone patients, but not the urine from those without stone and untreated control, cause stress-induced premature senescence and telomere shortening in proximal renal tubular cells similar to the positive control, hydrogen peroxide. They also report that the mechanism underlying such senescence induction may be mediated *via* p16 up-regulation and down-regulation of shelterin components.

An animal study by Jin et al. employs a wide variety of techniques to determine the landscape of renal immune cell population in glyoxylate-induced kidney stone model. They demonstrate that short chain fatty acids (SCFAs) prevent glyoxylate-induced kidney stone formation by increasing $CX3CR1^{+}CD24^{-}$ macrophage population and decreasing $GR1^{+}$ neutrophil infiltration in the kidney. Moreover, a mechanistic study reveals that such preventive effects of SCFAs is mediated through GPR43, one of the receptors for SCFAs.

A clinical study by Kumar et al. underscores significant impact of diets on the immunity and immune response in kidney stone disease. They show that the high-oxalate diet affects monocyte bioenergetics, mitochondrial complex activity, cytokines/chemokines profile and inflammatory signaling in humans. However, the clinical impact and final outcome of such immunomodulation in kidney stone modulation remain to be elucidated.

Overall, the knowledge offered in these articles is beneficial to build a clearer picture of the immunity and immune response in kidney stone disease. However, more extensive investigations on this Research Topic are still required to further enhance our understanding of the pathogenic mechanisms of kidney stone disease with an ultimate goal to reduce new and recurrent stone formation and to lessen its complications.

AUTHOR CONTRIBUTIONS

All the authors edited this Research Topic, wrote and reviewed this article, and approved it for publication.

FUNDING

VT is supported by Mahidol University and Thailand Science Research and Innovation (TSRI) (IRN60W0004). TY is supported by The Naito Foundation and JSPS KAKENHI Grant Number JP19H03791.

ACKNOWLEDGMENTS

We are grateful to all the authors and reviewers for their contributions to this Research Topic.

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